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Healthcare Costs and Impact of Medication Adherence on Outcomes in Patients on Novel Anticoagulant Therapy

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HEALTHCARE COSTS AND IMPACT OF MEDICATION ADHERENCE ON OUTCOMES IN PATIENTS ON NOVEL ANTICOAGULANT THERAPY

BY

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ABSTRACT

Introduction: Atrial fibrillation (AF) is a very common condition that causes cardiac rhythm disturbance and affects 2.7 to 6.1 million individuals in the United States (US). Warfarin, which is considered as a gold standard anticoagulant for the last 50 years to treat AF has limitations pertaining to the risk of bleeding, interaction with drugs and requires frequent monitoring. Novel Oral Anti-Coagulants (NOAC including dabigatran and rivaroxaban) are new promising drugs which have shown better or similar efficacy to lower stroke risk and fewer side effects compared to warfarin in the clinical trials. To compete with warfarin, NOACs may need to demonstrate substantial real-world evidence in regards to improving clinical outcomes and cost savings.

Objective:

The study was designed to evaluate the extent of undertreatment (adherence), and its predictors along with the impact of adherence on clinical outcomes, including ischemic stroke, bleeding, and Deep Vein Thrombosis and Pulmonary Embolism (DVTPE). Furthermore, the analysis helped to estimate the economic burden of NOACs vs. warfarin and identify specific subgroups with high-cost drivers and Healthcare Resource Utilization (HCRU) to achieve optimal benefits and devise strategies for cost-savings. The objective was achieved by conducting the following studies:

Study 1 - To examine patterns of medication adherence (measured by Proportion of Days Covered [PDC]) in patients with atrial fibrillation taking NOACs vs. warfarin for 6 or 12 months (post index). Furthermore, the study examined the short and long-term factors predicting adherence to the NOAC therapy after controlling potential confounders.

Study 2 - To examine the impact of adherence on the short and long-term risk of ischemic stroke, bleeding DVTPE and recurrent DVTPE in patients with AF taking NOACs during a one-year period (post index). The impact of adherence on outcomes was investigated by comparison of risk among propensity-matched adherence (adherent vs. non-adherent) cohorts.

Study 3 – To describe and compare the economic burden (cost and HCRU) in patients using NOACs vs. warfarin therapy. Furthermore, the study aimed to identify specific subgroups and key drivers of high-costs and HCRU. The final aim of the study was to explore if there are any differences in cost/HCRU between adherent and non-adherent NOAC patients.

Methods: The research utilized a retrospective cohort study design. Atrial fibrillation patients (ICD-9-CM codes 427.31/32), with ≥2 prescription fills for NOAC or warfarin, CHA_2DS_2VASC score ≥1, and 6-months pre-index continuous enrollment from the Optum® Clinformatics™ Data Mart (Optum Insight, Eden Prairie, MN) (Jan 1, 2010 and Dec 31, 2012) were included. The index date was the first prescription claim for NOAC or warfarin. Adherence was calculated using Proportion of Days Covered (PDC) over a 1-year period. Predictors of adherence (PDC ≥ 80%) were examined using a logistic regression model controlling for the covariates including age, gender, stroke risk, co-morbidities, insurance type, region, pre-index cardiac drug use (beta-blocker, Angiotensin II receptor blockers [ARB] or Angiotensin-converting enzyme [ACE] inhibitor, statin), etc. For the second study, adherent (PDC ≥ 80%) and non-adherent patients were matched on the above covariates using propensity score (Inverse Probability Treatment Weighting). The adjusted risk estimates were obtained at 6 and 12

months using a Cox proportional hazards model or generalized linear models (Poisson, negative Binomial) and compared across adherence based matched cohorts. In the final study, the economic value in terms of adjusted healthcare costs (inpatient, outpatient, and drug costs) and HCRU was estimated using a GLM model with gamma distribution and compared between patients taking NOACs vs. warfarin. Unadjusted costs were presented using descriptive analysis by subgroups based on demographic and clinical characteristics (age, gender, Charlson's comorbidity index (CCI), insurance type, CHA_2DS_2VASC score, region, pre-index cardiac drug use, including beta-blocker, ARB-ACE inhibitor, statin use). Cost specific to bleeding events were calculated as an exploratory analysis. Similarly, the costs and HCRU were descriptively compared between the adherent and non-adherent patients taking NOACs.

Results: A total of 5057 (N=1770 NOAC vs. N=3287 warfarin) patients with mean age of 66 years were included in the cohort based on the inclusion and exclusion criteria. For a 12-month follow-up, the proportion of adherent (PDC ≥80%) patients were higher among NOACs users (78.42%) compared to warfarin users (61.88%). Using multivariate logistic model controlling for the confounders; Age, CCI and statin use were major predictors of both short (6-month) and long-term (12-month) adherence to NOACs. The CHA_2DS_2VASC score was significantly associated with the short-term adherence while but not associated with the long-term adherence.

For 12-month of adherence assessment, the three cohorts for bleeding, ischemic stroke, and DVTPE included 1617, 1651, 1739 patients (N=3440 for recurrent DVTPE at 6-month assessment). For 12-month drug use, the incidence of bleeding, ischemic stroke, and DVTPE was 4.21%, 3.11%, and 1.11% respectively. Based on the multivariate

analysis at 6 and 12 months of adherence assessment, the non-adherence was significantly associated with 1.72 and 1.94 times increase in the stroke risk respectively. Similarly, non-adherence was found to be significantly associated with elevated risk of recurrent DVTPE 3 and 6 months and DVTPE risk at 3, 6, 9 months. The risk of bleeding in non-adherent patients was slightly lower (HR= 0.84 – 6 months, HR= 0.94 – 12 months) but not significant compared to the risk of bleeding in adherent patients.

High annual drug cost for NOAC users ($4988 vs. $331) was offset by higher medical (inpatient and outpatient) costs for warfarin users (Total annual cost for warfarin $31,400 vs. $22,134). The mean of annual ER visits (14 vs. 13) and office visits (76 vs. 49) was also higher for warfarin users compared to the patients taking NOACs.

Overall, among warfarin users, female patients had higher HCRU, patients from the South had higher medical costs and office visits. Highest cost drivers for drug cost for warfarin users was patients from Northeast. Conversely, highest cost drivers for medical cost were patients less than <65 years and patients with CCI +3.

For NOACs, the highest cost driver for the drugs was user who were 65 and above, from Northeast, $CHA_2DS_2VAS_C$ >2 (mod-high risk), and independent insurance. Additionally, medical cost was driven by EPO insurance and CCI+3.

Although medical costs and HCRU were lower for adherent vs. non-adherent patients taking NOACs, the differences were non-significant.

Conclusion: Use of NOACs due to its better adherence compared to warfarin may help prevent inadequate anticoagulation and complications. Determining the factors influencing the adherence such as age, CCI, and stroke risk can help plan targeted

approaches and interventions to improve adherence. Our results can help healthcare providers and managed care organizations to recognize the importance of adherence to NOAC medications among patients to prevent clinical risks including stroke, DVTPE and bleeding events. The study provides a valuable estimate of the economic burden in AF patients using NOACs and warfarin. These cost estimates can be further used as inputs in the studies involving cost-effectiveness analysis and indirect treatment comparisons. We found the higher drug costs for NOACs were offset by lower inpatient costs, outpatient costs, and HCRU; which can lead to overall monetary savings to the patient taking NOACs and to the healthcare system. Overall, the conducted research provides comprehensive evidence to help support NOACs as an optimal treatment choice for the AF patients.

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PREFACE

To the reader: This document follows the manuscript format and is composed of 3 manuscripts.

MANUSCRIPT 1 - MEDICATION ADHERENCE AND ITS PREDICTORS AMONG ATRIAL FIBRILLATION PATIENTS USING WARFARIN, DABIGATRAN AND RIVAROXABAN IN UNITED STATES.

MANUSCRIPT 2 - SHORT AND LONG TERM IMPACT OF MEDICATION ADHERENCE ON RISK OF STROKE, BLEEDING AND DVTPE IN ATRIAL FIBRILLATION PATIENTS USING NOVEL ANTICOAGULANTS (DABIGATRAN AND RIVAROXABAN)

MANUSCRIPT 3 – DISTRIBUTION OF COSTS AND HEALTHCARE UTILIZATION FOR OUTCOMES IN PATIENTS USING NOACS (DABIGATRAN & RIVAROXABAN) AND WARFARIN

TABLE OF CONTENTS

LIST OF TABLES

TABLE PAGE

LIST OF FIGURES

FIGURE PAGE

LIST OF APPENDIX

MANUSCRIPT I

MEDICATION ADHERENCE AND ITS PREDICTORS AMONG ATRIAL FIBRILLATION PATIENTS USING WARFARIN, DABIGATRAN AND RIVAROXABAN IN UNITED STATES

Formatted for submission to the Value in Health journal, not yet submitted.

ABSTRACT

Introduction: The prevalence of atrial fibrillation (AF) in the United States (US) is 2.7 to 6.1 million and is a leading cause of stroke (fivefold risk in AF patients). Novel Oral Anti-coagulants (NOACs including Dabigatran and Rivaroxaban) are new promising drugs with better or similar efficacy to lower stroke risk and fewer side effects compared to warfarin in the clinical trials. Adherence to the medication therapy is crucial in improving efficacy, reducing the costs and hospitalizations. Since the therapy is relatively new, very few studies have examined the medication adherence to NOACs and its pattern over time. This observational study captured the medication adherence and its trend in the NOAC users vs. warfarin users using Proportion of Days Covered (PDC) over a period of 12 months in a real-world setting. Furthermore, the study examined short and long-term factors associated with medication adherence to NOACs.

Method: A retrospective cohort study was conducted utilizing data from the Optum® Clinformatics™ Data Mart (Optum Insight, Eden Prairie, MN) database between January 1, 2010, and December 31, 2012. The study population was identified based on documentation of ≥ 1 diagnosis of atrial fibrillation or flutter ICD-9 code 427.31/32, age ≥18 years and $CHA_2DS_2VAS_C$ score ≥1. Adherence was calculated using PDC as (*Total Number of days covered by NOAC drugs as a class/ Number of days between index prescription date to the end of the calendar year, disenrollment, or death*) for 3, 6, 9 and 12 months. The patient was defined as 'adherent' if PDC was ≥80%. Predictors of adherence (1= PDC ≥80%, 0=<80%) were evaluated at 6 and 12 months using the logistic regression model controlling for age, gender, insurance type, pre-index cardiac drug use (beta-blocker, Angiotensin-II receptor blocker [ARB] or Angiotensin-converting

enzyme [ACE] inhibitor, statin), CHA_2DS_2VASC score and Charlson's Comorbidity Index (CCI).

Results: A total of 5057 (N=1770 NOAC vs. N=3287 warfarin) patients with a mean age of 66 years were included in the cohort based on the inclusion and exclusion criteria. For a 12-month follow-up, the proportion of adherent (PDC ≥80%) patients were higher among NOACs users (78.42%) compared to warfarin users (61.88%). Similarly, the patients using NOACs were consistently more adherent than warfarin users for 3, 6, 9 and 12 months of adherence assessment. The proportion of adherence among NOAC users was high at 3-months assessment (84.30%) and declined over time [6 months (82.80%), 9 months (76.45%)]. A similar pattern of decrease in adherence over time was observed for warfarin users. Using multivariate logistic model controlling for the confounders; Age (OR=1.030, 95% CI 1.015-1.045), a CCI score of < 2 (OR= 1.460, 95% CI 1.108-1.923), and statin use were positively associated ($p \leq 0.05$) with an increase in medication adherence for 12 months among NOAC users. For short term NOAC use (6 months), patients with low-risk (based on the CHA_2DS_2VASC score of 1,2) were 27% less likely to adhere to the NOAC treatment (OR = 0.725 95% CI 0.580-0.907) compared to the high-risk patients (CHA_2DS_2VASC score of ≥3).

Conclusion: Overall, patients taking NOACs have better (short and long-term) adherence to the therapy compared to warfarin users. Age, CCI and statin use were major predictors of both short and long-term adherence to NOACs. The CHA_2DS_2VASC score significantly associated with short-term adherence while statin use was specifically associated with long-term adherence to NOACs. The results obtained from the study will help clinicians and healthcare providers to understand the use of these (especially

NOACs) drugs in a real-world setting and help implement therapy in practice to provide optimal benefits to the patients. Further research on subgroups and their treatment patterns (including switching) is warranted.

BACKGROUND

Atrial Fibrillation and Prevalence

Atrial Fibrillation (AF) is a common condition causing cardiac rhythm disturbance due to structural or electro-physical abnormality resulting in abnormal impulse formation.[1] In 2010, the prevalence of AF in the United States (US) was 2.7 to 6.1 million and is expected to grow between 5.6 and 12 million in 2050.[2,3] Approximately 70% of patients with AF are of the age between 65-85 years.[4] AF can be caused by ischemic heart disease, heart failure, hypertension while other causes of AF may include hyperthyroidism, acute infection, alcohol withdrawal, or post-surgery. The symptoms manifested in AF may include palpitation, dizziness, sweating, and shortness of breath.[5] AF is one of the key risk factors for ischemic stroke, increasing the risk up to 5-fold and accounts for one-third of all hospitalizations in the US for cardiac rhythm disturbances.[6]

Treatment of Atrial Fibrillation

Treatment options for AF primarily include antiplatelet, anticoagulant, beta blockers, calcium channel blockers, sodium and potassium channel blockers.[7] Anticoagulants significantly decrease symptoms and health outcomes in AF leading to greater benefits.[8] Anticoagulants prevent blood clots and are used to treat existing blood clots.

Anticoagulants and their use in AF

Warfarin is an oral vitamin K-antagonist approved in 1954 and has been a gold standard of care for more than 50 years. It acts on multiple sites in the clotting cascade by preventing the synthesis of main coagulation factors, including II, IX, VII, and X by inhibiting vitamin K-dependent γ-carboxylation to work as an anticoagulant.[9] Warfarin as an anticoagulant has shown to reduce the risk of stroke, myocardial infarction, and

death. In a randomized clinical trial (RCT) of 973 patients aged 75 years or over in the United Kingdom (UK), the risk of hemorrhage was significantly ($p \leq 0.05$) lower for warfarin (1.4%) compared to aspirin (1.6%) [10,11].

The variable dosing, frequent dose adjustments and narrow window for therapeutic use in warfarin have prevented it's the widespread use in patients. Moreover, drug-interactions with concomitant medications, change in the diet, and the need for periodic monitoring has made warfarin use challenging for clinicians and patients. Due to these restrictions, many AF patients cannot use warfarin.[12] In some patients, warfarin cannot be administered due to other factors such as non-response, poor adherence, unwanted side-effects, etc. The unmet need can be fulfilled using Novel Oral Anticoagulants (NOACs) which have recently proven to exhibit better efficacy, safety, and convenience compared to the existing warfarin treatment.

Novel Oral Anti-Coagulants (NOACs)

NOACs include two newly approved oral drugs, dabigatran "Pradaxa" (2010) and rivaroxaban "Xarelto" (2011). Dabigatran was the first oral anticoagulant approved in the US by the Food and Drug Administration (FDA) in 50 years. It acts as a thrombin inhibitor and is indicated for reducing the risk of stroke, systemic embolism, treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in AF patients. In an RCT involving 18,113 patients with a primary outcome being the stroke (of any type), the risk of hemorrhagic strokes with dabigatran was also significantly (74%) lower than that of warfarin.[13] Dabigatran is given as a fixed dose of 110 or 150 mg twice daily, and requires negligible monitoring and has a peak effect in 1-2 hours as opposed to 4-5 days in warfarin.[14]

Rivaroxaban was the first oral factor Xa inhibitor approved by the FDA. In ROCKET-AF trial (**R**ivaroxaban **O**nce-Daily, Oral, Direct Factor Xa Inhibition **C**ompared with Vitamin **K** Antagonism for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation) with 14,264 patients, rivaroxaban was non-inferior to warfarin in annual rates of stroke and systemic embolism (1.7% versus 2.2%) [15]. Similar to dabigatran, rivaroxaban has a rapid onset of action, requires twice daily dosing and has lower side effects compared to warfarin. Apaxiban and edoxaban, both factor Xa inhibitors were approved in December 2012, and January 2015 respectively. Based on the data availability for our study (2010 to 2012 only), apaxiban and edoxaban will not be included as a part of the hypothesized research plan.

Overall, NOACs have shown better or similar efficacy compared to warfarin in the clinical trials. Few benefits of NOACs include quick time-to-peak effects, fewer drug to drug and dietary interactions, fixed dosing regimens, and requires little monitoring. Now the reversal antidotes for NOACs (idarucizumab, andexanet alfa) are available. Disadvantages of NOACs include an inability to administer to patients with a prosthetic heart valve or stage V chronic kidney disease.[12]

Adherence and NOACs

Adherence has been defined as "An active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result".[16,17] Osterberg categorized measurement of adherence into indirect (pill count, prescription count, Medication Event Monitoring Systems [MEMS] cap, questionnaires) and direct method (directly observed therapy, metabolite in blood, and biological marker in the blood)[17].

Since their (NOACs) launch in 2010-2011, there has been limited literature published on "real-world adherence to the NOACs" using large observational studies. For oral anticoagulants based on the "Randomized Evaluation of Long-term Anticoagulant Therapy" (RELY) trial, the discontinuation rates at 1 year (using pill count) for dabigatran, and warfarin were 15.5%, and 10.2%, respectively. In the ROCKET AF trial, discontinuation rates were similar between rivaroxaban and warfarin groups (15.7% vs. 15.2%). Although it is essential to acknowledge that trial data has some limitations as the adherence reported in the trials is calculated in a controlled environment.

Study Rationale and Justification

A small number of studies have reported adherence using different methods (MPR, PDC, Persistence gap of 60 to 180 days) for NOACs.[18-22] Although the clinical guidelines recommend the use of NOACs for anticoagulation, the utilization of dabigatran and rivaroxaban remains sub-optimal in the real-world. Adherence to the medication therapy is crucial in improving the efficacy, reducing the costs and hospitalizations. Since the NOAC therapy is relatively new, it is not yet widely accepted and prescribed as warfarin by clinicians and healthcare providers.

Not many studies have examined the medication adherence of NOACs and its patterns over time. This observational study captured medication adherence (NOACs vs. warfarin) and its trend using Proportion of Days Covered (PDC) over a period of 12 months in a real-world setting. Furthermore, short and long term predictors of adherence to NOAC therapy were evaluated. The results obtained from the study will help clinicians and healthcare providers to understand the use of these drugs in a real-world

setting and help make a suitable therapeutic choice in practice to provide optimal benefits to the patients.

Hypothesis: Ho = There is no statistical difference in estimate of medication adherence between AF patients taking NOACs and warfarin.

METHODOLOGY

Study Design

This was a retrospective cohort study to compare adherence between NOAC and warfarin users and examine its patterns over a one-year period.

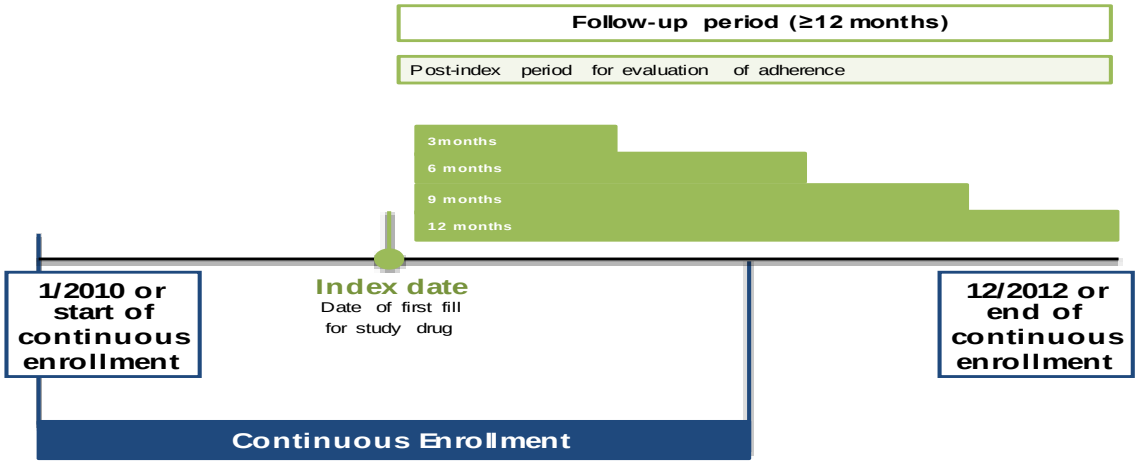
The study was conducted using commercial insurance de-identified claims data from January 1, 2010, to December 31, 2012, using a large-scale US managed care health plan affiliated to Optum® Clinformatics™ Data Mart (Optum Insight, Eden Prairie, MN) database. The primary outcome of the study was adherence calculated using PDC at 3, 6, 9 and 12 months and assessment of predictors of adherence at 6 and 12 months.

Data Source: The database mainly includes medical claims and pharmacy claims data. It contains details on dates of service, place of service, International Classification of Diseases, Ninth Revision, (ICD-9) diagnosis codes, provider type, National Drug Code (NDC), drug quantity dispensed, days supplied, charges, deductibles, and copayments. The large US health plan database includes 14 million patients and 500,000 Medicare enrollees. The member file constitutes the demographic data and eligibility information. The database also includes a drug file, a medical file (outpatient), standard pricing file (cost) and a confinement file for inpatient data. The database comprehensively covers diverse geographical areas of the US. All study data were accessed using Health Insurance Portability and Accountability Act (1996) compliant protocols. To ensure the patient confidentiality, no identifiable protected health information was used or analyzed during the study.[23] The data was accessed using the server at the University of Rhode Island (URI) and analyzed using SAS EG 7.1. The study was also approved by an Institutional review board at URI.

Sampling design/procedures: All patients between January 1, 2010, to December 31, 2012, were identified. Patients with warfarin, dabigatran or rivaroxaban (NOACs) were identified using the NDC codes and brand name using REDBOOK. The index date was defined as the date of first prescription fill of the NOAC or warfarin in their respective drug cohort. Patients with at least two claims for the study drugs in the post-index period were included. Patients were included based on at least one AF or atrial flutter diagnosis claim identified using the medical file (inpatient or outpatient) with an ICD-9 code of 427.31/427.32 during the pre-index period or 30 days within the index date. In addition to the AF patients, subjects with atrial flutter were also included since a large proportion of patients with atrial flutter also suffer from atrial fibrillation (overlap) and the recommended treatment is similar for AF and flutter for the prevention of stroke. Patients with age $\geq$ 18 years were included. Patients with concomitant use of warfarin and NOAC during the post-index assessment period were excluded. Few patients previously used warfarin in the pre-index period prior to starting the NOACs. Since, NOACs are also prescribed to fulfill the unmet need in few patients with prior warfarin use, to avoid exclusion of any NOAC user (and sample size considerations), the inclusion of these patients was based on the definition of "warfarin naïve." Based on the definition of 'warfarin naïve' in RELY trials, a patient was defined 'warfarin naïve' if there was no use of warfarin 2 months before the index date (first fill) of the NOAC or if the NOAC was used for a duration of at least 5 or more months.[24] This criterion was to ensure that we capture all NOAC users and avoid any potential bias in regards to prior warfarin therapy for assessment of outcomes. For sensitivity analysis, we also examined no use of warfarin 100 days before the index date as a threshold. Thus, the index date of these

"warfarin naïve" users was based on the first prescription fill of NOACs. Data based on RELY trials showed no heterogeneity between patients who had prior warfarin use (based on the above definition) and those with no prior warfarin therapy. Age was used as a continuous variable. Furthermore, patients with CHA_2DS_2VASC score ≥1 (1-9) were identified using ICD-9 codes. CHA_2DS_2VASC characterizes the risk of stroke based on a score composed of (congestive heart failure, hypertension, age >75 years, diabetes, prior stroke, pulmonary or vascular disease, age [65-74 years], sex [as female]) (Please refer to Appendix Table 1 for ICD-9 codes and variable categorization). The patients with at least 6 months of pre and post index continuous eligibility with a permissible gap of 45 days were included in the cohort. Patients with hyperthyroidism (ICD-9 242.9) were excluded from the patient cohort since it may be the probable cause of AF but is not related to cardiac pathways.

Figure 1.1: Study design and timeline



Measurement of Adherence

The medication possession ratio (MPR) and PDC are the most frequently used measures to estimate adherence. The denominator in MPR is defined based on the difference between first and the last fill and doesn't account for discontinuation of the drug. Furthermore, overestimation of MPR might occur due to early refill and if patients take concurrent medications of the same class. PDC is the most favored method to measure adherence in the recent years since it accounts for non-persistence where the denominator is days between first fill and end of the study.[25]

Definition of Outcome

Adherence was calculated using PDC as follows =

Numerator: Number of days covered by NOAC drugs as a class (using fill date and supply days); at least 2 fills were required to calculate the PDC. The days were truncated if days of supply went beyond the study period. "The PDC calculation also considered when patient refilled their medication before exhausting the previous fill by adjusting the

prescription start date to be the day after the previous fill ends".[26] *The fills beyond the study period were truncated.*

Denominator: Number of days between index prescription date to the end of the calendar year, disenrollment, or death.

$$\frac{\text{Proportion of Days Covered}}{\text{End of study date} - \text{first prescription fill date}}$$

For calculation of PDC, patient's measurement period was defined as the index prescription date to the end of the assessment period, disenrollment, or death.

Data Analysis:

Adherence was presented for NOACs users and warfarin users as PDC ranging from 0-100%. PDC above 100 was truncated to 100% (e.g., If a patient has a PDC of 110%, the patient was still considered as 100%. No patient was excluded based on the PDC truncation).[27] Categorical analysis was performed to present frequency and percentage of patients with adherence (PDC) ≥80% across the 2 groups (NOACs users vs. warfarin users). Adherence was assessed at 3, 6, 9, 12 months of use.

Secondly, the descriptive characteristics were analyzed and compared across adherent and non-adherent cohorts using NOAC therapy.

Finally, multivariate logistic regression was performed to investigate the predictors of adherence among NOAC patients ($Y = \alpha+\beta1X1 + \beta2X2 + \beta3X3 + \ldots\ldots\ldots\ldots+ \beta iXi + €$). Adherence using PDC (dependent variable) ≥80% and < 80% was coded as 1 and 0 respectively. Demographic variables, including, gender, age (continuous variable), region, Charlson's Comorbidity Index (CCI 0, 1-2, >2 based on parametric assessment), $CHA_2DS_2VAS_C$ score (1-2 as low-risk, >2 as high-risk groups)[28] were used as covariates. Pre-index cardiac medications were selected based on American Heart Association

(AHA) medication classes recommended for AF therapy. Furthermore, these drug classes (beta-blockers, Angiotensin-II Receptor Blocker [ARB] or Angiotensin-converting enzyme [ACE] inhibitors, and statins) were as covariates in the pivotal dabigatran trial. The type of insurance was also evaluated as possible confounders. First, the adherence (DV) was tested separately against each covariate using bivariate analysis. Univariate logistic regression was performed for the continuous variables and association with categorical variables was tested using a chi-square test. Possible confounders were identified, and their association with adherence was examined (with p-value ≤ 0.25). Due to the clinical significance, CHA_2DS_2VASC score was considered as a major confounder and was retained in the final model.

Next using the basic model, the multicollinearity between the variables of interest was tested to check whether the regressor variables are similar (in direct linearity) to other regressor variables. The collinearity was examined using the condition number (if >30 then collinearity exists) and the proportion of variance statistics for the eigenvalues. The multicollinearity was tested by examining the Variance Inflation Factor (VIF) for the variables. A VIF > 5 indicates collinearity among variables. Only one of the two or more collinear variables was selected for inclusion in the final multivariate model.

Moreover, the predictive model was primarily built using 2 methods 1. Automatic backward elimination process and 2. Manual Elimination process for sensitivity analysis. Using the automatic backward elimination process, the model with the preliminary set of variables was refined by sequentially removing variables which do not contribute to the model. It was performed as an iterative process to predict adherence by examining Wald p-values, with confirmation through likelihood ratio testing (p-value > 0.05 confirming

exclusion). This backward elimination process was repeated until a basic model was obtained. Similar to backward elimination, variables were manually evaluated by elimination of the non-significant variable based on Wald p-values. Once eliminated, the model was iteratively re-ran with the remaining variables and the process was continued until a parsimonious model with only significant covariates was obtained.

Furthermore, all two-way interactions between CHA_2DS_2VASC and other independent variables were also investigated for possible synergistic relationships. Significant interaction terms were retained. As a part of sensitivity testing, the model with independent variables + interaction term of CHA_2DS_2VASC score with each independent variable (one at a time) was examined. Comparison of models was also performed using Akaike Inclusion Criteria (AIC – lower is better). Moreover, the goodness of fit of the models was examined by Hosmer-Lemeshow test.[29] If p-value ≥ 0.05, the model fit is good. Model fit statistics were evaluated examining -2 log-likelihood estimate. Larger -2log-likelihood estimate indicated a poorly fitted model.

Results from the final parsimonious model were presented with the help of adjusted odds ratios along with their 95% CI, and p-values obtained from two-sided tests with a significance level of p-value ≤ 0.05.

For sensitivity analysis, predictors of short-term adherence (at 6-month assessment) to NOACs were also investigated.

RESULTS

We found a total of 25,120 users of NOACs and 149,359 users of warfarin within the study period. A total of 14,618 NOAC and 120,607 warfarin users had 2 or more

prescription fills. Out of 14618 NOAC patients, 4332 patients had a prior warfarin use in the pre-index period, and the definition of 'warfarin naïve' was used to screen the patients. Based on the definition of 'warfarin naïve', 1107 out of 4332 patients were included as NOACs. The sensitivity analysis using a threshold of 100 days instead of 60 days led to a very minor change in the sample size and hence threshold of 60 days was retained and used. A total of 1032 patients were excluded due to an overlap (concomitant use of warfarin and NOACs) in the post-index period. Based on the other inclusion criteria (diagnosis of atrial fibrillation in pre-index period or 30 days within the index date, ≥18 years, continuous enrollment for 6 months pre and post-index, and CHA2DS2VASc ≥1), a total number of warfarin and NOAC patients were 8130 and 4758 respectively. Based on 6 months of drug use a total number of 3,453 NOAC users and 5596 warfarin users were included in the analysis. At 12 months of the assessment period (drug use), the study sample consisted of 5057 patients. A total of 1770 NOAC patients and 3287 warfarin patients met the inclusion and exclusion criteria and were included in the final analysis cohort. Figure 1.1 in Tables and Figures describes the cohort sample selection in detail.

Baseline Characteristics among NOAC and Warfarin patients

Based on the study sample of 5057 patients, the mean age of the sample was 66 years with more men (66.7%) than females. Most of the patients were either from the South or the Midwest (65%). Most of the patients (65%) were categorized as moderate to high-risk of stroke based on CHA_2DS_2VASC score >2. Over 80% of patients in the cohort had CCI above 0. For medication use, statins were the most frequently used drugs (50% of patients) followed by beta-blockers used by more than 25% of the sample.

Based on the chi-square test, most of the patient characteristics were different across the NOACs and warfarin. More than 50% of NOAC users were from the South (vs. 37% for warfarin users). For the stroke risk based on the CHA_2DS_2VASC score, a higher proportion of warfarin users had a moderate-high risk (more severe) compared to NOAC users (67% vs. 60%). Most of the patients had CCI score > 1(85%) where patients on warfarin therapy were slightly severe (with a higher proportion of 3+ comorbidities) compared to the NOAC users (48% vs. 34%). The use of statins was high in both cohorts (>50% of the patients). Please refer to Table 1.1 in Tables and Figures.

Adherence measured by PDC

Adherence was measured at 3, 6, 9 and 12 months post the index date. Overall, NOAC patients had a higher adherence (PDC ≥80%) to the treatment as compared to the warfarin therapy. At 12 months of follow-up, the proportion of adherent patients using NOAC was 78.42% (N=1388/1770) compared to 61.88% (N=2034/3287) for warfarin patients. The trend for higher adherence in NOACs vs. warfarin was preserved for 3, 6, 9-month assessment period. Table 1.2 in Tables and Figures I compare the adherence measured at different time points between NOAC and warfarin cohorts. The proportion of adherence among NOAC patients at 3 months was (N=2859/3453) 84.30% and declined over time (82.80% for 6 months and 76.45% 9 months). Similarly, the proportion of adherence among warfarin users at 3 months was 77.43% (N=5224/6747) followed by 72.61% and 61.88% for at 6 and 9 months respectively.

Baseline Characteristics among Adherent and Non-Adherent NOAC patients

For the cohort based on the drug usage for 12 months, the patient demographic and clinical characteristics were summarized for adherent vs. non-adherent NOAC users at baseline (index date). Age, CHA_2DS_2VASC score, type of insurance, and use of statins were significantly ($p \leq 0.05$) different across the adherent and non-adherent patients. The mean age of patients was 65 years with adherent (66 years) patients being older than the non-adherent (62 years) patients. The cohorts consisted of more men (69.3%) than women (30.7%). The majority of patients were from the South (51.3%) or the Midwest (21.9%), and more than 60% of the final cohort received point-of-service (POS) insurance.

There were 39.4% patients with a CHA_2DS_2VASC score of 1-2 (low risk) and 38.8% with a CHA_2DS_2VASC score > 2 (termed as a moderate-high risk of stroke). Patients with moderate-high risk of stroke (based on the CHA_2DS_2VASC score) were more adherent to medications compared to the low-risk patients. The CCI scores were well distributed across adherent and non-adherent patients. In regards to the cardiac medication use, statins and beta-blocker use were higher among adherent patients compared to the non-adherent patients. Table 1.3 in Tables and Figures I describes the patient demographic and clinical characteristics in detail among adherent and non-adherent NOAC patients.

Bivariate Analysis

The bivariate analysis between adherence and independent variables was initially performed to select the variables needed in the multivariable model. Variables with an association and a cut-off threshold of $p \leq 0.25$ were included for further analysis. Age, insurance type, region, CHA_2DS_2VASC score, statin and beta-blocker use was associated

with the adherence to the therapy. Table 1.4 in Tables and Figures I describes the significance estimates for the bivariate analysis.

Prior to building the multivariate model, multicollinearity was examined using the eigenvalues (<10), conditional index (<35) and Variance Inflation Factor (<3).

Multivariate analysis

A multivariate logistic regression was modeled to examine the predictors of adherence for 12-month assessment in NOAC patients. The dependent variable was adherence (1,0), and age, CHA_2DS_2VASC score, Charlson's comorbidity index (CCI), region, insurance type, statin use, beta blocker use was selected as covariates based on the bivariate analysis. CHA_2DS_2VASC Score, Charlson's comorbidity index were included irrespective of association (in the bivariate analysis) due to their clinical significance. The parametric assessment was performed on the variables to assess the distributional characteristics. The CHA_2DS_2VASC score was categorized as low risk (1-2) and moderate-high risk (>2). The CCI was also categorized as (0, 1-2 and ≥3). Based on the preliminary backward elimination model, age, CCI, insurance type, statin use and monthly drug cost were significantly associated.

A final model consisted of all significant variables from the backward elimination model and CHA_2DS_2VASC score. The final model converged with an Akaike Inclusion Criteria (AIC) of 1800.21. Hosmer-Lemeshow (goodness of fit) was 0.5393 ($p>0.05$). The c-statistic was 0.627. (Tables and Figures I – Table 1.4).

Based on the final model, age (OR-1.030, 95% CI 1.015-1.045), a CCI score of < 2 (OR-1.460, 95% CI-1.108-1.923), and statin use were positively associated with an increase in medication adherence. (Table 1.4 in Tables and Figures I). The final model was further

tested for diagnostics to examine the Pearson's and chi-square residuals. The top 5 outliers based on the Cook's distance were removed, and the model was re-examined for any considerable change in the estimates and inference. Since the change was minor and did not significantly affect the model outputs, the 5 observations were added back to the final model.

Although not statistically significant at 12 months, low-risk patients based on the CHA_2DS_2VASC score were less likely to be adherent to NOAC therapy compared to high-risk patients.

Sensitivity analysis at 6 months

Using the same model building procedure, predictors of adherence were examined for short-term NOAC use (6 months). At 6 months, age, CCI and statin use remained consistently significant as seen in multivariate analysis for 12 months. Additionally, it was found that CHA_2DS_2VASC score and region were significant predictors ($p \leq 0.05$) of adherence to NOACs for short term use. The patients with low risk (based on the CHA_2DS_2VASC score of 1,2) were 27% less likely to adhere to the treatment (OR-0.725 95% CI 0.580-0.907). Please refer to Table 1.5 Tables and Figures and Appendix I Table 3 for the complete model.

DISCUSSION

Our analysis found higher adherence to NOAC therapy as compared to warfarin over a 1-year period. This result was consistent over the short and long-term when examined at 3, 6, 9 and 12-month interval. The adherence decreased over time in both the cohorts (NOAC vs. Warfarin).

Unadjusted estimates suggested age, insurance type, region, CHA_2DS_2VASC score, statin, and beta-blocker use was associated with the adherence to the therapy. For multivariate analysis controlling for the covariates, an increase in age, fewer co-morbidities, and statin use led to better adherence whereas low-risk CHA_2DS_2VASC led to lower adherence. It was interesting to know that CHA_2DS_2VASC score and region was significantly associated with short-term adherence to NOACs, but not long-term, whereas statin use was not influential predicting adherence based on both short and long term use. Our study was the first to examine the patterns of short and long-term NOAC use and assess predictors of adherence among a large nationwide database in a real-world setting.

Many observational studies have shown an estimate of adherence to NOAC therapy is variable ranging from 40-88%.[30,31] However, the assessment of adherence has been done in different settings, including clinics, self-reported, public claims database, commercial claims databases including IMS, MarketScan, Humana, etc. with varying assessment period (2010-2014).[30,32-34] The estimate of adherence to NOACs found in our study (78.4%) is consistent with other database studies. Similar studies have attempted to understand the adherence of NOACs over a period of 3, 6, 12 and 24 months, and have shown higher adherence of PDC ≥ 80% (approximately 75%) for assessment shorter time intervals of 3 months after the index date and the adherence decreased over time (63% for 12 months).[32]

In an observational study of Veteran Affairs (VA) cohort of 5,376 patients with AF initiated on dabigatran, 72% of patients had the proportion of days covered (PDC) ≥ 80%. Moreover, the mean PDC reported was 84% ± 22%.[34] In another retrospective study evaluating electronic medical and pharmacy records within the University of California

(UC) Davis Medical Center with 400 patients, the mean MPR for patients using dabigatran was 0.63. Overall, 43% of the patients taking dabigatran had an MPR of < 0.80. The study found gender (female), and PRN (prescription as necessary) medication use as predictors of low adherence among patients.[18] In another nationwide observational study in Denmark with 2960 patients, 1-year PDC for dabigatran was 84%.[19] The PDC for rivaroxaban and dabigatran using Healthcare claims from the Humana database between July 2013 and December 2014 was >65%.[33] Another study using IMS Health's LifeLink Health Plan Claims Database from 2010 to 2012 found mean MPR as 0.73 and 40% patients with adherence above ≥ 0.80.[30]

In a study using US Department of Defense administrative claims data, the persistence rate (with a gap defined by ≥ 60-day discontinuation) for dabigatran versus warfarin was 72% versus 53% for 6 months and 63% versus 39% for 1 year respectively.[20] In a German study of 1204 patients, discontinuation rates of rivaroxaban in daily care for stroke prevention in atrial fibrillation (SPAF) patients were approximately 15% in the first year and very low thereafter.[22] Furthermore, persistence (no gap of => 60 days) was compared between rivaroxaban and warfarin in a US based study using MarketScan data (2010-2013). Patients were more persistent to rivaroxaban (77%) as compared to warfarin (58%).[35]

Our study found higher age, the risk of stroke (CHA_2DS_2VASC score >2), statin use, and lower CCI scores as major predictors of adherence consistent with the previous literature.[20,22,36,37] Younger age, male as a gender, low stroke-risk, poverty, higher education and poor cognitive function, have also been found to be associated with lower adherence. Another recent study based on the Danish patient registry reported an overall

1-year PDC equal to 83.9 % and found that females (OR-1.06), patients using cardiovascular drugs and $CHA_2DS_2VASC \geq 2$ (OR-1.12) were major predictors of adherence among dabigatran users.[19]

Numerous studies have reported discontinuation of NOACs is primarily due to bleeding-related side effects. In a study on 467 Chinese patients in a clinic, dyspepsia was the most common cause of discontinuation, followed by adverse events and bleeding events including gastrointestinal bleeding and intracranial hemorrhage. Furthermore, dosing frequency, lack of laboratory monitoring, fear of side effects, and cost were other minor causes of discontinuation of therapy.[38] In addition to understanding the relative impact of anticoagulants-associated complications (such as bleeding), future research should emphasize on creating greater awareness and partnership between patient and physician for better decision making around anticoagulation.[39]

The OPTUM database is a large nationwide database and provided sufficient sample size to interpret results robustly. However, claims data can lead to selection bias due to imprecise billing codes. Moreover, it should be acknowledged that OPTUM is mostly a commercial database under-represented by the elderly population (above 65 years). Over 65% the sample was represented by males, predominantly from the South or the Midwest and the database lacked information in regards to the race, ethnicity, and reason for discontinuation of therapy.

Although the clinical variables (e.g. INR values, ventricular ejection fraction, body mass index) were not included in the dataset, clinical determinants such as CHA_2DS_2VASC and CCI helped to control for disease severity by considering hypertension, prior cardiovascular disease, diabetes and other co-morbidities. The claims data lacks

information regarding reasons for discontinuation or side-effects due to the drug which might help explain non-adherence estimates. Furthermore, adherence assessment based on 3, 6, 9, and 12-month windows might lead to truncation of the data. Therefore, the adherence assessment windows were kept close at every 3 months. It is also important to understand that the dosing of warfarin is variable and frequently adjusted. We also looked at the distribution of days of supply to explore a potential bias. The distribution of the days of supply for warfarin and NOACs was primarily around 30 and 60-day dosing which substantiated that the therapies might be comparable. Prior use of cardiac drugs was also accounted, and selection of the drugs was based on AF therapy recommended by American Heart Association (AHA).[40] These drugs were also used as covariates to understand the individual effects in the dabigatran pivotal trials. However, aspirin use was not comprehensively captured in the claims database due to its availability as over the counter (OTC) drug. The differences in the descriptive characteristics might be explained by the fact that NOACs might be prescribed to patients who have unmet need after warfarin therapy, this might lead to potential channeling or selection bias, in our study we did not control the selection bias using propensity scores.

Sensitivity analysis helped to confirm the results over a short and long-term period. To eliminate the bias in regards to variable follow-up time, adherence was assessed for patients who had medication use at regular intervals up to 3, 6, 9, and 12 months.

CONCLUSION

Overall adherence to NOACs is suboptimal and decreases over time. Patients taking NOACs have higher (short and long-term) adherence to the therapy compared to warfarin

users. Age, CCI, and statin use were major predictors of both short and long-term adherence while CHA_2DS_2VASC score was associated with short-term adherence but not with long-term adherence. The short and long-term estimates of adherence to NOACs and associations observed in our study may help the healthcare providers and managed care organizations to strategize and provide optimal care to the patients by improving adherence to reduce clinical complications, healthcare resource use, and costs. Further research on individual drugs using matched cohorts and their treatment patterns (including switching) is warranted.

TABLES AND FIGURES I

Figure 1.2: Cohort Selection based on Inclusion and Exclusion Criteria

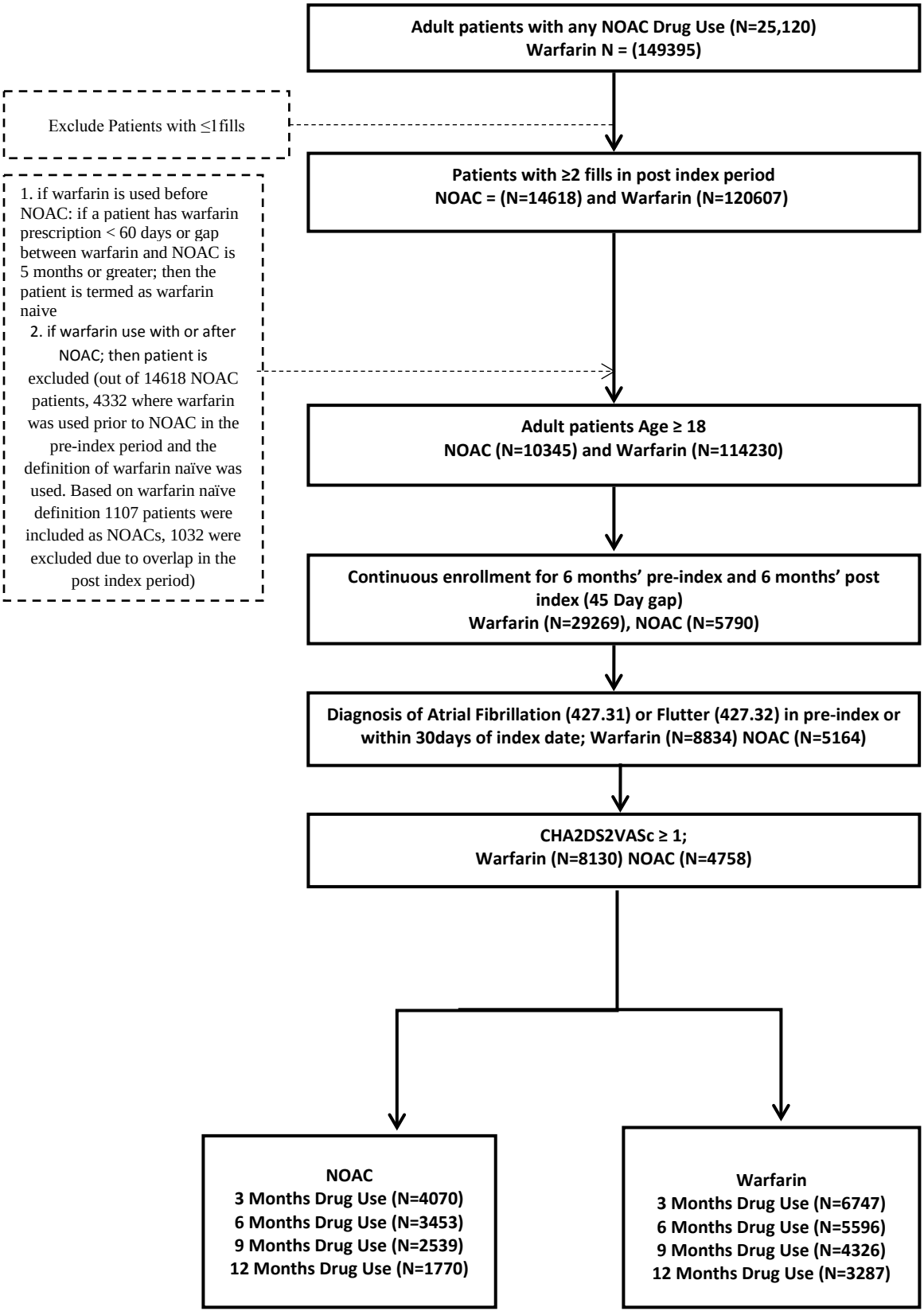


Table 1.1 Patient Demographic and Clinical Characteristic of NOAC vs Warfarin patients at 12-month assessment period

Variable Description	Statistic Response Category	Total (N= 5,057)	NOACs (N= 1,770)	Warfarin (N= 3,287)	P-value (Chi-sq)
Age at index date	N	5057	1,770	3,287	<0.001
	Mean (SD)	65.94 (11.61)	65.2 (10.56)	66.34 (12.13)	
	Median(IQR)	64 (58-75)	64 (59,73)	65 (58,76)	
	Range	18-86	26,86	18,86	
Gender	Female	1,718 (33.97)	544 (30.73)	1,174 (35.72)	0.0004
	Male	3,339 (66.03)	1,226 (69.27)	2,113 (64.28)	
Insurance type	EPO	512 (10.12)	204 (11.53)	308 (9.37)	
	HMO	312 (6.17)	103 (5.82)	209 (6.36)	
	IND	1,030 (20.37)	280 (15.82)	750 (22.82)	
	Others	7 (0.14)	0 (0.00)	7 (0.21)	
	POS	2,945 (58.24)	1,104 (62.37)	1,841 (56.01)	
	PPO	251 (4.96)	79 (4.46)	172 (5.23)	
Region	Midwest	1,469 (29.05)	388 (21.92)	1,081 (32.89)	<0.001
	Northeast	534 (10.56)	168 (9.49)	366 (11.13)	
	South	2,134 (42.20)	908 (51.30)	1,226 (37.30)	
	West	920 (18.19)	306 (17.29)	614 (18.68)	
Stroke risk (CHA2D2VASC)	low risk	1,762 (34.84)	697 (39.38)	1,065 (32.40)	<0.001
	mod-high risk	3,295 (65.16)	1,073 (60.62)	2,222 (67.60)	
CCI category	CCI score 0	715 (14.14)	311 (17.57)	404 (12.29)	<0.001.
	CCI score 1-2	2,140 (42.32)	851 (48.08)	1,289 (39.22)	
	CCI score 3 and+	2,202 (43.54)	608 (34.35)	1,594 (48.49)	
Statin use	Yes	2478(49.0)	917(51.81)	1561 (47.49)	0.003
	No	2579 (51.0)	853 (48.19)	1726 (52.51)	
ACE ARB Inhibitor	Yes	2382 (47.10)	874 (49.38)	1508 (45.88)	0.017
	No	2675 (52.90)	896 (50.62)	1779 (54.12)	
Beta-blocker	Yes	1392 (27.53)	536(30.28)	856 (26.04)	0.001
	No	3665 (72.47)	1234 (69.72)	2431(73.93)	

CCI- Charlson's comorbidity Index, HMO – Health maintenance organization, PPO- Preferred provider organization, EPO - Exclusive provider organizations, IND- Independent, POS-Point of service, ARB- Angiotensin Receptor Blocker, ACE- Angiotensin-converting enzyme

Table 1.2 Adherence Measured by PDC at Different Time-points

Adherence	N	Adherence NOACs	N	Adherence Warfarin	p-value
3 months	4070	3431 (84.30%)	6747	5224 (77.43%)	<0.001
6 months	3453	2859 (82.80%)	5596	4063 (72.61%)	<0.001
9 months	2539	1941 (76.45%)	4326	2677 (61.88%)	<0.001
12 months	1770	1388 (78.42%)	3287	2034 (61.88%)	<0.001

*PDC $\geq$ 80 = Adherent patient, Adherence measured by PDC at different time points

Table 1.3 Patient Demographic and Clinical Characteristics of Adherent Vs Non-adherent NOAC patients at 12-month Assessment Period

Variable Description	Statistic Response Category	Total (N= 1,770)	Adherent (N= 1,388)	Non-Adherent (N= 382)	p-value
Age at index date	N	1770	1,388	382	<.0001
	Mean (SD)	65.20 (10.55)	66.02 (10.16)	62.24 (11.42)	
	Median(IQR)	64 (59, 73)	64 (59,73)	62 (55,68)	
	Range	26,83	34,86	26,86	
Gender	Female	544 (30.73)	426 (30.69)	118 (30.89)	0.9407
	Male	1,226 (69.27)	962 (69.31)	264 (69.11)	
Insurance type	EPO	204 (11.53)	143 (10.30)	61 (15.97)	<0.001
	HMO	103 (5.82)	73 (5.26)	30 (7.85)	
	IND	280 (15.82)	239 (17.22)	41 (10.73)	
	POS	1,104 (62.37)	862 (62.10)	242 (63.35)	
	PPO	79 (4.46)	71 (5.12)	8 (2.09)	
Region	Midwest	388 (21.92)	317 (22.84)	71 (18.59)	0.0487
	Northeast	168 (9.49)	132 (9.51)	36 (9.42)	
	South	908 (51.30)	689 (49.64)	219 (57.33)	
	West	306 (17.29)	250 (18.01)	56 (14.66)	
Stroke risk (CHA2D2VASC)	Low risk	697 (39.38)	515 (37.10)	182 (47.64)	0.0002
	Mod-high risk	1073 (60.62)	873 (62.90)	200 (54.36)	
CCI Category	CCI score 0	311 (17.57)	239 (17.22)	72 (18.84)	0.5734
	CCI score 1-2	851 (48.08)	676 (48.70)	175 (45.81)	
	CCI score 3 and+	608 (34.35)	473 (34.08)	135 (35.34)	
Statin Use	No	853 (48.19)	636 (45.82)	217 (56.81)	0.0001
	Yes	917 (51.81)	752 (54.18)	165 (43.19)	
ACE ARB Inhibitor Use	No	896 (50.62)	688 (49.57)	208 (54.45)	0.0910
	Yes	874 (49.38)	700 (50.43)	174 (45.55)	
Beta-blocker Use	No	1,234 (69.72)	980 (70.61)	254 (66.49)	0.1213
	Yes	536 (30.28)	408 (29.39)	128 (33.51)	

Variable Description	Statistic Response Category	Total (N= 1,770)	Adherent (N= 1,388)	Non-Adherent (N= 382)	p-value

CCI- Charlson's comorbidity Index, HMO – Health maintenance organization, PPO- Preferred provider organization, EPO - Exclusive provider organizations, IND- Independent, POS-Point of service, ARB- Angiotensin Receptor Blocker, ACE- Angiotensin-converting enzyme

Table 1.4 Logistic Regression Model to examine Predictors of Adherence in NOAC Patients at 12 Months

Variables	Odds ratios	95% Wald Confidence Limits		p-value
Age	1.030	1.015	1.045	<.0001
CCI - CCI score 0 vs CCI score 3 and+	1.275	0.879	1.850	0.2011
CCI - CCI score 1-2 vs CCI score 3 and+	1.460	1.108	1.923	0.0072
CHADS2VASC - low risk vs mod-high risk	0.859	0.644	1.146	0.3010
Insurance type - EPO vs PPO	0.354	0.158	0.791	0.0114
Insurance type - HMO vs PPO	0.328	0.139	0.774	0.0109
Insurance type - IND vs PPO	0.517	0.229	1.170	0.1134
Insurance type - POS vs PPO	0.523	0.245	1.118	0.0946
Statin use - No vs Yes	0.703	0.553	0.892	0.0038

Note: Dependent Variable = Adherence (1,0), Independent Variables = Age, CHADS2VASC Score, Charlson's Comorbidity Index, Insurance Type, Drug Use, Drug Cost (Statin Use, Ace Inhibitor Use, Beta Blocker Use, ARB Use)
Interactions: All Independent variables with CHADS2VASC Score were tested and compared against a model without interaction. Final model selection was based on goodness of fit and AIC.

Table 1.5 Logistic Regression Model to examine Predictors of Adherence in NOAC Patients at 6 Months

Effect	Odds Ratio	95% Wald Confidence Limits		p-value
Age	1.030	1.019	1.040	<.0001
CCI Category - CCI score 0 vs CCI score 3 or + 3	1.448	1.080	1.942	0.0133
CCI Category - CCI score 1-2 vs CCI score 3 or +3	1.276	1.026	1.587	0.0287
CHA2D2VASC - low risk vs mod-high risk	0.725	0.580	0.907	0.0048
Region - Midwest vs West	0.840	0.610	1.156	0.2838
Region - Northeast vs West	0.895	0.604	1.327	0.5812
Region - South vs West	0.694	0.524	0.919	0.0109
Statin use - No vs Yes	0.763	0.633	0.918	0.0042

Note: Dependent Variable = Adherence (1,0), Independent Variables = Age, CHADS2VASC Score, Charlson's Comorbidity Index, Insurance Type, Drug Use, Drug Cost (Statin Use, Ace Inhibitor Use, Beta Blocker Use, ARB Use)
Interactions: All Independent variables with CHADS2VASC Score were tested and compared against a model without interaction. Final model selection was based on goodness of fit and AIC.

APPENDICES I

Appendix I: Table 1 ICD-9 Diagnosis Codes

		ICD-9 Codes
AF Diagnosis	Atrial Fibrillation and Flutter	427.31, 427.32
	Hypothyroidism	240.9
CHA2DS2VASC Score	Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.x, 518.4
	Diabetes	250.x, 357.2, 362.0, and 366.41
	Hypertension	401.x, 402.x, 403.x, 404.x, and 405.x
	Stroke/ TIA	433,434, 435, 436
	Vascular disease	410,411,412, 413, 414, 443.8, 443.9
Major Charlson's Comorbidity Index diagnosis	Myocardial Infarction	410, 412
	CHF	428
	Cerebrovascular disease	430-438
	COPD	490-496, 500-505, 506.4
	Paralysis	342, 344.1
	Chronic Renal failure	582, 585, 586, 588, 583.0 – 583.7
	Ulcers	531-534
	Cirrhodites	5712, 5714, 5715, 5716
	AIDs	042,044
	Metastatic tumor	196.0-199.1, 196.x

Rothendler JA, Rose AJ, Reisman JI, Berlowitz DR, Kazis LE. Choices in the use of ICD-9 codes to identify stroke risk factors can affect the apparent population-level risk factor prevalence and distribution of CHADS2 scores. American Journal of Cardiovascular Disease. 2012;2(3):184-191.
http://healthcaredelivery.cancer.gov/seermedicare/program/charlson.comorbidity.macro.txt

Appendix I: Table 2 Logistic Regression Model to examine Predictors of Adherence in NOAC Patients at 12 months

AIM 1 MODEL FINAL_OCT.rtf

Appendix I: Table 3 Logistic Regression Model to examine Predictors of Adherence in NOAC Patients at 6 months

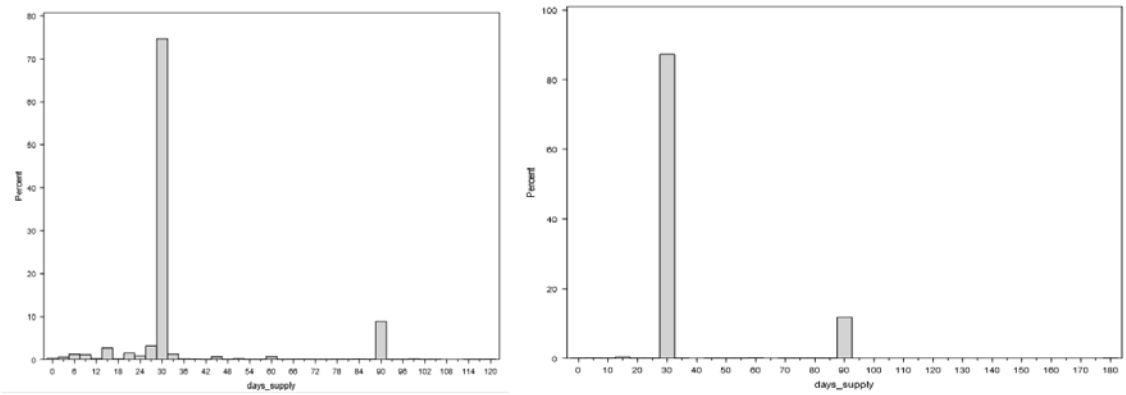
AIM 1 MODEL FINAL_OCT 6M.rtf

Appendix I: Table 4 Logistic Regression Model to examine Predictors of Adherence in NOAC Patients at 12 months (with Interactions)

AIM 1 (LR model with interactions at

Appendix I: Table 5 Distribution of days of supply variable for warfarin and NOACs

a) . WARFARIN (left) and NOAC (right) graph:



Appendix I: Table 6 Model Diagnostics

AIM 1 (LR Model Diagnostics Plots).d

Appendix I: Table 7 Variable Information

Variable	*Type*	*Coding*
Charlson's Comorbidity Index	*Categorical*	*0=CCI score 0* *1=CCI score 1-2* *2=CCI score 3 or more*
CHASD2SVASC Score	*Categorical*	*1=low risk (1-2)* *2=mod-high risk (>2)*
Region	*Categorical*	*STATES CT,ME,MA,NH,RI,VT,NJ,NY,PA = Northeast* *IN,IL,MI,OH,WI,IA,KS,MN,MO,NE,ND,SD = Midwest* *DE,DC,FL,GA,MD,NC,SC,VA,WV,AL,TN,KY,MS,AR,LA, OK,TX = South* *AZ,CO,ID,NM,MT,UT,WY,NV,AK,CA,HI,OR,WA = West*
Insurance Type	*Categorical*	*EPO=1* *HMO=2* *IND=3* *OTH=4* *POS=5* *PPO=6*
Age	*Continuous*	*NA*
Beta blocker Use *ARB Use* *Statin Use* *Ace Inhibitor Use*	*Categorical*	*1= Yes* *0=No*
Gender	*Categorical*	*1 =Male , 0 =Female*
Monthly Drug Cost	*Categorical*	*1= ≤$400, 2=>$400*

Appendix I: Table 8 Distribution of CHAD2VASC Score and CHADS2VASC

	Drug			
CCI Index	***Warfarin N%***	***NOAC N%***	***Total %***	
0	*404 (12.29)*	*311 (17.57)*	*715*	*14.14*
1	*648 (19.71)*	*442 (24.97)*	*1090*	*21.55*
2	*641 (19.50)*	*409 (23.11)*	*1050*	*20.76*
3	*502 (15.27)*	*242(13.67)*	*744*	*14.71*
4	*364(11.07)*	*172 (9.72)*	*536*	*10.6*
5	*264(8.03)*	*89 (5.03)*	*353*	*6.98*
6	*214 (6.51)*	*61 (3.45)*	*275*	*5.44*
7	*123 (3.74)*	*25 (1.41)*	*148*	*2.93*
8	*76 (2.31)*	*11 (0.62)*	*87*	*1.72*
9	*33 (1.00)*	*7(0.40)*	*40*	*0.79*
10	*13 (0.40)*	*0 (0.00)*	*13*	*0.26*
11	*2 (0.06)*	*1 (0.06)*	*3*	*0.06*
12	*1 (0.03)*	*0 (0.00)*	*1*	*0.02*
15	*2 (0.06)*	*0 (0.00)*	*2*	*0.04*
Total	*3287*	*1770*	*5057*	
CHADS Score	***Warfarin N%***	***NOAC N%***	***Total***	***%***
1	*436 (13.26)*	*278 (15.71)*	*714*	*14.12*
2	*629 (19.14)*	*419 (23.67)*	*1048*	*20.72*
3	*729 (22.18)*	*374 (21.13)*	*1103*	*21.81*
4	*572 (17.40)*	*314 (17.74)*	*886*	*17.52*
5	*429 (13.05)*	*177 (10.00)*	*606*	*11.98*
6	*262 (7.97)*	*126 (7.12)*	*388*	*7.67*
7	*157 (4.78)*	*60 (3.39)*	*217*	*4.29*
8	*61 (1.86)*	*18 (1.02)*	*79*	*1.56*
9	*12 (0.37)*	*4 (0.23)*	*16*	*0.32*
Total	*3287*	*1770*	*5057*	

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MANUSCRIPT II

SHORT AND LONG TERM IMPACT OF MEDICATION ADHERENCE ON RISK OF STROKE, BLEEDING AND DVTPE IN ATRIAL FIBRILLATION PATIENTS USING NOVEL ANTICOAGULANTS (DABIGATRAN AND RIVAROXABAN)

Formatted for submission to the Circulation: Cardiovascular Quality and Outcomes journal, not yet submitted.

ABSTRACT

Introduction: Novel Oral Anti-coagulants (NOACs including Dabigatran and Rivaroxaban) are new promising drugs which have shown better or similar efficacy to lower stroke risk and have fewer side effects compared to warfarin in the clinical trials. It has been substantially studied that better adherence to cardiac medications tends to reduce strokes and other related outcomes. Prevention of stroke and other clinical outcomes can help reduce hospitalizations and its related burden on the healthcare system. To date, there have been very few studies which established a relationship between short and long-term adherence to NOACs and the reduction of ischemic stroke, major bleeding, Deep Venous Thrombosis and Pulmonary Embolism (DVTPE) and recurrent DVTPE risks. This research was the first to compare the impact of adherence on the stroke, bleeding, DVTPE and recurrent DVTPE risk in a propensity score based matched sample over a one-year period.

Methods: A retrospective cohort study was conducted utilizing de-identified data from Optum® Clinformatics™ Data Mart (Optum Insight, Eden Prairie, MN) (Jan 1, 2010 and Dec 31, 2012). database between January 1, 2010, and December 31, 2012. The study population was identified based on documentation of ≥ 1 diagnosis of atrial fibrillation or flutter ICD-9 code 427.31/32, 2 or more prescriptions of NOACs, age ≥18 years and CHA_2DS_2VASC score ≥1. Adherence was calculated using PDC at 6, 9 and 12-month assessment periods. Patients were defined as adherent (≥80%) or non-adherent (<80%) and matched based on propensity score using Inverse Probability Treatment Weighting (IPTW). The risk of ischemic stroke, major bleeding DVTPE, and recurrent DVTPE was

calculated in post adherence assessment period and compared across groups. Adjusted estimates were derived using Cox and GLM model controlling for age, gender, region, CHA_2DS_2VASC score, Charlson's Comorbidity Index (CCI), drug use at baseline, and insurance type.

Results: The sample matched by IPTW provided better matching compared to caliper matching. At 12-month of adherence assessment, the three cohorts for bleeding, ischemic stroke, and DVTPE included 1617, 1651, 1364 patients respectively. The mean age of the sample was 65 years, 70% of the sample were males, and there was a higher proportion of patients with a CHA_2DS_2VASC score of 2 (23%). At 12 months, the incidence of bleeding, ischemic stroke, and DVTPE was 4.21%, 3.11%, and 1.11% respectively. Based on the multivariate analysis at 6 and 12 months of adherence assessment, the non-adherence was significantly associated with 1.7 and 1.9 times increase in stroke risk respectively. Similarly, non-adherence was found to be significantly associated with elevated risk of recurrent DVTPE 3 and 6 months and DVTPE risk at 3, 6, 9 months. The risk of bleeding in non-adherent patients was slightly lower (HR 0.84 – 6 months, 0.94 – 12 months) than risk in patients who are adherent to the NOACs.

Conclusion: Impact of adherence on the reduction of stroke and DVTPE risk is noteworthy. The risk of bleeding is not significantly different between adherent and non-adherent patients. Further studies on longer follow-up are warranted.

BACKGROUND

Atrial Fibrillation (AF) is a common condition causing cardiac rhythm disturbance due to electro-physical or structural abnormality resulting in abnormal impulse formation.[1]

In 2010, the prevalence of AF in the United States (US) was 2.7 to 6.1 million and is expected to grow between 5.6 and 12 million in 2050.[2,3] Approximately 70% of patients with AF are between 65-85 years of age.[4] AF is one of the key risk factors for ischemic stroke, increasing the risk up to 5-fold.[5]

Stroke Risk and AF

Stroke is the number four cause of mortality and a leading cause of long-term disability in the US. In the US, the stroke led to 1 in every 19 deaths in 2009, and a total treatment cost is estimated to be $38.6 billion per year.[6] A stroke is caused due to an abrupt disruption of blood supply to the brain, which may be caused due to the bursting of the blood vessels (hemorrhagic stroke) or blocking by a clot (ischemic stroke).[7] The risk factors for developing a stroke include, but not limited to, older age, cigarette smoking, obesity, cardiovascular disease and diabetes. One such heart-related condition, AF, an irregular heart rhythm, is a significant risk factor.[8]

Recent estimates in the US has AF affecting an estimated 2.6 to 3 million Americans with more than 795,000 people having a recurrent or a new stroke each year.[9,10]

The risk of stroke due to AF also increases with older age, rising from 1.5 % in patients with an age of 50 to 59 years to 23.5 % for 80 to 89 years old patients.[5]

Deep Venous Thrombosis and Pulmonary Embolism Risk (DVTPE)

According to Center for Disease Control (CDC) estimates, 900,000 people are affected by DVTPE every year, which accounts for 60,000-100,000 deaths [11]. DVT is caused

when there are clots in veins and PE is caused in continuation when the clots disintegrate and enter the arteries. The incidence of the DVTPE increases with age to 1 in 100 in patients above the age of 80. Together they are termed as Venous Thrombo-Embolism (VTE). Chronic disease, cancer, obesity, age, surgery, trauma, infection are some of the risk factors for DVTPE.[12]

Patients with AF and stroke tend to develop DVTPE. Hence, the use of anticoagulants as a preventative therapy for DVTPE and recurrent DVTPE is recommended.[13] Low molecular weight heparin, fondaparinux and VKA anticoagulants (warfarin) are also used as pharmacological treatments.[14] Lately, NOACs have shown promising results in a trial setting and are now approved for prevention of recurrent DVTPE.

Bleeding Risk

The use of anticoagulants is always associated with risk of bleeding-related complications. The difference in risk of bleeding was found to be non-significant between rivaroxaban and warfarin in the ROCKET-AF clinical trials (3.32 vs. 3.57).[15] Similar results with higher (but not significantly different) rates of bleeding with dabigatran were found compared to the warfarin.[16] Major bleeding (including intracranial hemorrhages, GI bleeding, etc.) and its related costs lead to an enormous burden on the healthcare system. Also, based on a recent assessment by FDA adverse event systems, the NOACs have been associated with a high number of bleeding-related adverse events but the information on risk factors and age is unavailable. A limited number of real world studies have presented the evidence of a non-significant difference between warfarin and NOACs in regards to the bleeding risk.[17] It is important to quantify

the bleeding risk in NOACs using real world data and understand the impact of adherence on the risk of bleeding.

Risk Stratification

The CHADS2 score has been used to quantify the risk of stroke or VTE in AF patients. It constituted a score of 0-6 based on risk factors for stroke including congestive heart failure (C), hypertension (H), , age > 74 years (A), diabetes (D) constituting 1 point each and previous occurrence of transient ischemic attack (TIA) or stroke with 2 points (S2).[18] The Antithrombotic Therapy and Prevention of Thrombosis, 9th edition, American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines published in 2012 recommended aspirin as the antithrombotic agent of choice for AF patients at low risk of stroke (CHADS2 = 0), and oral anticoagulant therapy (OAC) for patients at intermediate to high risk of stroke (CHADS2 $\geq$ 1).[19] Recently, based on the ACC/AHA/ESC guidelines (2006) for the management of patients with AF; CHADS2 has been updated to CHA_2DS_2VASc (scored 0-9) which adds three more factors: vascular events or disease (V), age 65–74 years (A), and female gender (Sc). The risk stratification is necessary for the AF patients since underuse of anticoagulants is prevalent in the high-risk population.[20] Mostly clinician and patients tend to prefer to prescribe aspirin which is a safer and cheaper alternative to OAC. Therefore, it is essential to assess the risk, for selection of appropriate treatment to achieve maximum benefits.

Use of NOACs in stroke and DVTPE

Medication options in AF include antiplatelets, anticoagulants, beta blockers, calcium channel blockers, sodium and potassium channel blockers.[21] Anticoagulants significantly

decrease symptoms and health outcomes and are responsible for improved overall health.[22] Warfarin is an oral vitamin K-antagonist approved in 1954 and has been a gold standard of care for more than 50 years. The variable dosing, frequent dose adjustments and narrow window for therapeutic use in warfarin therapy have prevented its the widespread use in patients. Moreover, interactions with concomitant medications, dietary restrictions, and the need for periodic monitoring has made warfarin use challenging for prescribers and patients.[14]

NOACs include newly approved oral drugs: dabigatran "Pradaxa" (2010) and rivaroxaban "Xarelto" (2011), apaxiban and edoxaban. Overall, NOACs have proven to have better or similar efficacy in terms of reduction of stroke risks and non-inferior to warfarin for risk of bleeding complication. NOACs are also prescribed to prevent recurrent DVTPE.[23] The American Academy of Family Physicians and the American College of Physicians guidelines for VTE recommends 3 to 6 months of anticoagulant therapy following the first occurrence of a DVTPE.

Relationship of Adherence with Stroke and Bleeding Risk

Retrospective observational studies have shown evidence that adherence to cardiovascular medications can reduce the hazard of stroke.[24-26] According to an observational study with 73,527 patients on hypertensive medications in Finland, at 10 years of follow-up, non-adherent patients had 3.01 (95% CI: 2.37–3.83) times higher odds of stroke death compared to adherent patients [25]. The REasons for Geographic And Racial Disparities in Stroke (REGARDS) was a prospective, longitudinal cohort study with 30,239 subjects in US aged ≥45 years, concluded that non-adherent patients (based on Morisky scale) had 1.08 (1.04–1.14) times greater risk of stroke compared to the

patients who were adherent to the antihypertensive medications.[27] For vitamin K antagonists (VKAs), non-adherence have been reported in the range of 22–58%.[28] According to a recent study including 4,188 Kaiser Permanente (US) patients with AF, more than 1 in 4 patients (26%) on warfarin discontinued therapy in the first year of therapy despite a low bleeding rate of 2.3%.[29] In a retrospective matched cohort study on 7539 patients with Kaiser Permanente Colorado (KPCO), the nonadherence to warfarin INR monitoring was associated with a modestly higher risk of thromboembolism (adjusted Hazard Ratio [HR] = 1.51; 95% confidence interval = 1.04 – 2.20).[30] In a study including 13,289 patients between January 2003 and December 2007 using Thomson Reuters MarketScan Research Database, estimated drug use in 3 cohorts: patients with no warfarin exposure vs. Low PDC (<80%) and high PDC (≥80%). Moreover, the incidence of ischemic stroke, transient ischemic stroke (TIA) and gastrointestinal bleeding (GI) was lower for patients with PDC ≥ 0.80 compared to patients with PDC < 0.80.[31]

Study Rationale and Justification

Adherence is pivotal to the success of the therapy and is a crucial to ascertain the risk-benefit of a recommended treatment. Although several studies have reported adherence to NOACs ranging from 40-94%, there is inadequate data on the impact of adherence on the stroke, bleeding, DVTPE and recurrent DVTPE risks. This study examined an association between adherence to NOACs and risk of ischemic stroke, bleeding and DVTPE and recurrent DVTPE over a short and long-term period. This study will be the first to match the adherent and non-adherent NOAC users based on propensity score to

compare the stroke, bleeding, DVTPE and recurrent DVTPE risks between the two cohorts.

Hypothesis: Ho = There is no statistical difference in risk of stroke/bleeding/recurrent DVTPE/DVTPE between equivalent cohorts based on adherence, matched using propensity score in AF patients taking NOACs.

METHODOLOGY

Study Design

A retrospective cohort study design was utilized to calculate the adherence to NOACs using PDC and examine its impact on stroke, bleeding and DVTPE risk in NOAC patients.

The study was conducted using medical and pharmacy claims data from January 1, 2010, to December 31, 2012, using a large-scale US managed care health plan affiliated to Optum® Clinformatics™ Data Mart (Optum Insight, Eden Prairie, MN) Inc. database. The primary outcome of the data was a stroke, bleeding, and recurrent DVTPE risk compared across propensity score-matched adherent and non-adherent cohorts.

Data source: The OPTUM database mainly includes medical claims, including inpatients and outpatient files and pharmacy claim data. It contains details on dates of service, place of service, International Classification of Diseases, Ninth Revision, Clinical Modification ICD-9-CM/ICD-10 diagnosis codes, provider type, National Drug Code-NDCs, drug quantity dispensed, days supplied, charges, deductibles, and copayments. The large US health plan database includes 14 million patients and 500,000 Medicare enrollees. The member file constitutes the demographic data and eligibility information. The database comprehensively covers diverse geographical areas of US with most of its enrollees from the South and the Midwest. All study data access was compliant with the Health Insurance Portability and Accountability Act. To ensure the patient's confidentiality, no identifiable protected health information was used or analyzed during the study.[32] The data was accessed using the server at the University of Rhode Island

(URI) and analyzed using SAS EG 7.1. The study was also approved by the Institutional review board at URI.

Sampling design/procedures: All patients between January 1, 2010, to December 31, 2012, were identified. Patients with warfarin, dabigatran or rivaroxaban (NOACs) were characterized using the NDC codes and brand name using REDBOOK. The index date was defined as the date of first prescription fill of the NOAC or warfarin in their respective drug cohort. Patients with at least two claims for the study drugs in the post-index period were included. Patients were included based on at least one AF or atrial flutter diagnosis claim identified using the medical file (inpatient or outpatient) with an ICD-9 code of 427.31/427.32 during the pre-index period or 30 days within the index date. In addition to the AF patients, subjects with atrial flutter were also included since a large proportion of patients with atrial flutter also suffer from atrial fibrillation (overlap) and the recommended treatment is similar for AF and flutter in terms of prevention of stroke. Patients with age $\geq$ 18 years were included. Patients with concomitant use of warfarin and NOACs during the post-index assessment period were excluded. Few patients previously used warfarin in the pre-index period prior to starting the NOACs. Since, NOACs are also prescribed to fulfill the unmet need in few patients with prior warfarin use, to avoid exclusion of any NOAC user (and sample size considerations), the inclusion of these patients was based on the definition of "warfarin-naïve." Based on the definition of 'warfarin naïve' in RELY trials, a patient was defined 'warfarin-naïve' if there was no use of warfarin 2 months before the index date (first fill) of NOACs or if the NOAC was used for a duration of at least 5 or more months.[33] This criterion was to ensure we capture all NOAC users and avoid any potential bias in regards to prior

warfarin therapy for assessment of outcomes. Thus, the index date of these "warfarin-naïve" users was based on the first prescription fill of NOACs. For sensitivity analysis, we also examined no use of warfarin 100 days before the index date as a threshold. Data based on RELY trials has shown no heterogeneity between patients who have prior warfarin use (based on the above definition) and those with no prior warfarin therapy. Age was used as a continuous variable. Furthermore, patients with CHA_2DS_2VASC score ≥1 (1-9) were identified using ICD-9 codes and included. CHA_2DS_2VASC characterizes the risk of stroke based on a score composed of (congestive heart failure, hypertension, age >75 years, diabetes, prior stroke, pulmonary or vascular disease, age [65-74 years], sex [as female]). Please refer to Appendix Table 1 for ICD-9 codes. The patients with at least 6 months of pre and post index continuous eligibility with a permissible gap of 45 days were included in the cohort. Patients with hyperthyroidism (ICD-9 242.9) were excluded from the patient cohort since it may be the probable cause of AF but is not related to cardiac pathways. (Please check Figure 2.1 in Tables and Figures II). Moreover, the final cohort was further sub-grouped based on each type outcome (Stroke, DVTPE, recurrent DVTPE, Bleeding) to avoid calculation of risk for competing outcomes. Patients in the cohort for recurrent DVTPE were defined based on a prior DVTPE occurrence in the pre-index period.

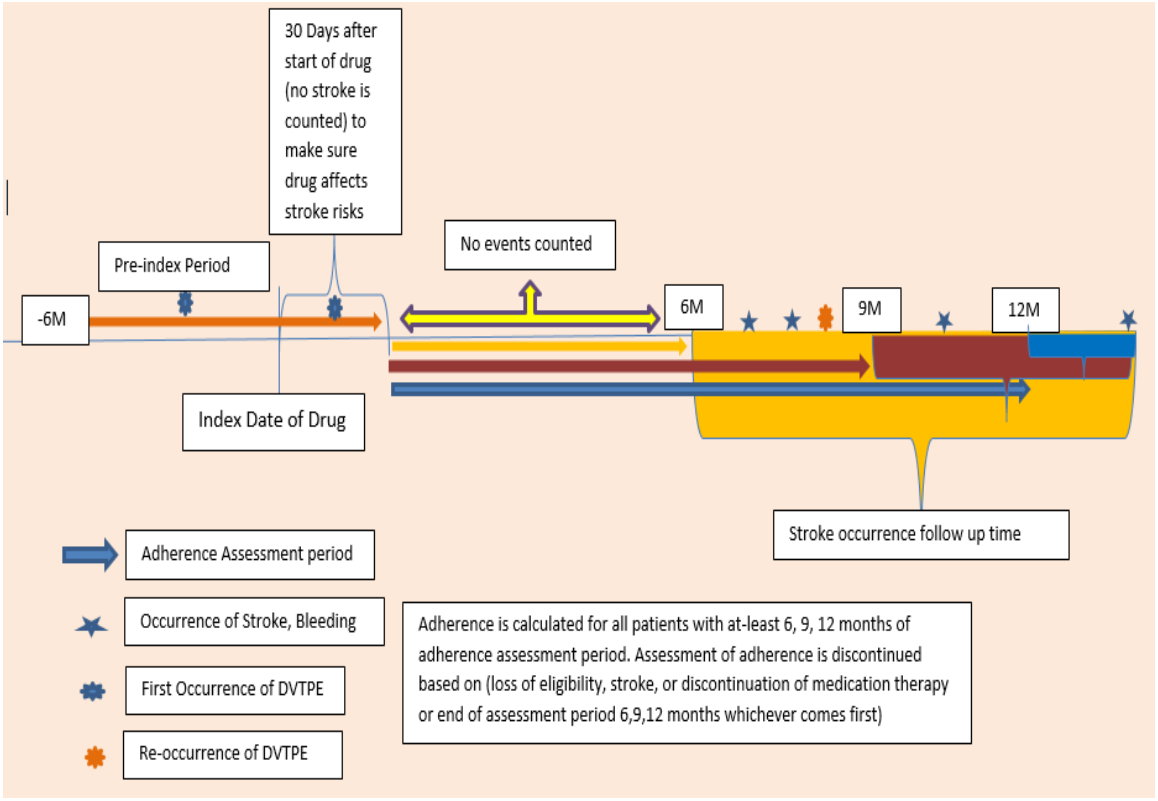
Definition of Outcome

The index date was defined as the date of the first prescription of NOACs. For calculation of PDC (exposure assessment), the patients were followed from one month after the index date to the end of assessment period (6,9,12 months) and were censored at the occurrence of an outcome (stroke, recurrent DVTPE, DVTPE and bleeding),

disenrollment from the healthcare plan, death, end of the study, whichever came first. Subjects with an outcome, such as ischemic stroke, DVTPE, bleeding between one month after the index date to the end of adherence assessment period (See figure 1) were excluded. These patients were excluded to avoid assessment of exposure and outcomes in the same time frame and to set a sequence where exposure (adherence) precedes the outcome to establish a causal relationship. Adherence was counted after first 30 days of drug use since it overlapped with the window for diagnosis of atrial fibrillation.

Outcomes were calculated from the end date of adherence assessment to outcome date, end of the study period or end of enrollment/death whichever occurred first. The patients were eligible to enter the cohort only once and were counted only for the first incident stroke, bleeding or post-index DVTPE episode. For assessment of recurrent DVTPE, only patients who had a previous DVTPE episode in the pre-index period (prior to the start of NOAC) were included in the cohort.

Figure 2.1: Study design and timeline



Cumulative incidence of the study outcomes was calculated, and relative risk (RR= Risk of outcome among exposed/Risk of outcome among unexposed) and its 95% CI was computed as a risk estimate.

The outcomes (ischemic stroke, major bleeding, DVTPE and recurrent DVTPE) were diagnosed based on ICD-9 codes (Please check the Appendix II Table 2.1 for a list of ICD-9) codes.

Measurement of Adherence

The medication possession ratio (MPR) and PDC are the most frequently used measures to estimate adherence. The denominator in MPR is defined based on the difference between first and the last fill and doesn't account for discontinuation of the drug. Furthermore, overestimation of MPR might occur due to early refill and if patients take concurrent medications of the same class. PDC is a preferred method to measure

adherence in the recent year since it accounts for non-persistence where the denominator is days between first fill and end of the study.[34] Adherence was calculated using PDC. Adherent patients were defined based on a cutoff of PDC ≥ 80%.

Propensity Score (PS) Matching

Patient cohorts (adherent vs. non-adherent) were matched based on the propensity score to reduce any confounding due to study covariates and control selection bias. The propensity score (PS) on stroke risk was calculated for each patient using a multivariate logistic regression controlling for covariates. Demographic variables including, gender, age (continuous variable), region, Charlson's Comorbidity Index (CCI 0, 1-2, >2 based on parametric assessment), CHA_2DS_2VASC score (1-2 as low-risk, >2 as high-risk groups)[35] were used as independent variables. Pre-index cardiac medication use was defined based on AHA medication classes recommended for AF therapy. Moreover, the medication drug classes were also used as covariates in the pivotal dabigatran trial. The type of insurance was evaluated as possible confounders. The c-statistic was examined to understand how well the predicted probabilities derived from the model classified the patients into their original groups.[36]

There are few ways to use the propensity score to compare outcomes: matching or stratifying patients on the PS, inverse probability of treatment, weighting using the PS, and covariate adjustment in subsequent multivariate regression models.[37] Matching is the most suitable method when the cases and control group are expected similar in size.[38] The patients were initially matched with 1:1 ratio using a specified caliper distance (e.g. equal to 0.02 of the standardized deviation of the logit of the propensity score).[39-42] Since the adherence was high (>70%) among the cohorts, to prevent loss of sample size; the

patients were matched "*with replacement*" of controls. Matching was evaluated by plots and by comparing descriptive characteristics. In our data, due to large number of pseudo-controls, optimum matching was not achievable using the caliper method.

Inverse probability Treatment Weighting was then used where the patients in the treatment (adherent) group were assigned a weight of the direct inverse of their propensity score, and the control group (non-adherent) group patients were assigned the inverse of the propensity score subtracted from 1.[43] The propensity weights were also trimmed for extreme values greater than 10. The truncation of extreme values helped achieve better matching of the weights.[44] The matching cohorts were compared using the plots and tabular results of the matched variables. The IPTW weights thus obtained were used in the multivariate models (Cox and GLM Models) to predict the effect of the exposure (adherence) on the outcomes (stroke, bleeding, DVTPE).

Multivariate models

Using the IPTW matched data for each cohort, the incidence of ischemic stroke, bleeding, DVTPE and recurrent DVTPE and mean follow-up time were calculated. To quantify the association of adherence to the ischemic stroke, bleeding, DVTPE and recurrent DVTPE risk multivariate model were used. The occurrence of an outcome (stroke, bleeding, DVTPE) was the dependent variable in the model and adherence was the primary independent variable. The Cox proportional hazard model or GLM models are preferred to calculate the relative risk.[45] The relative risk was compared and graphically plotted using Kaplan Meier graphs. For GLM models, binomial models restrict the probabilities of an outcome to be greater than or equal to zero and thus leads to convergence issues.[46] Since the occurrence of stroke, DVTPE and bleeding are rare (with <10% of the sample);

to avoid the convergence issues, negative binomial, and Poisson distributions were preferred for GLM models.[47] The models were checked for over-dispersion by checking the deviance and Pearson's chi-square and were scaled in the model as required. To control for different follow-up time for outcomes for each patient, a semi-parametric Cox proportional hazard model was used by matching the cohorts using IPTW weights. The data was right-censored. The Cox models were prior tested for proportionality of hazards by checking the Schoenfeld residuals, plots for log negative log of time and were evaluated for interaction with the adherence and time-varying covariate to check for the non-significant interaction term.

RESULTS

We found a total of 25,120 users of NOACs and 149,359 users of warfarin within the study period. A total of 14,618 NOAC and 120,607 warfarin users had 2 or more prescription fills. Out of 14618 NOAC patients, 4332 patients had a prior warfarin use in the pre-index period, and the definition of 'warfarin naïve' was used to screen the patients. Based on the definition of 'warfarin naïve', 1107 out of 4332 patients were included as NOACs. The sensitivity analysis using a threshold of 100 days instead of 60 days led to a very minor change in the sample size and hence threshold of 60 days was retained and used. A total of 1032 patients were excluded due to an overlap (concomitant use of warfarin and NOACs) in the post-index period. Based on the other inclusion criteria (diagnosis of AF in pre-index period or 30 days within the index date, ≥18 years, continuous enrollment for 6 months pre and post-index, and CHA2DS2VASc ≥1), a total number of warfarin and NOAC patients were 8130 and 4758 respectively.

To ascertain individual discontinuation dates (non-competing) for assessment based on each distinct occurrence of an outcome (stroke, bleeding, recurrent DVTPE and DVTPE) for each subject separately, 4 cohorts based on 4 outcomes were created. For cohort with the outcomes such as a major bleeding, the total number of patients at 6, 9 ,12 months of adherence assessment were 3285, 2353 and 1617. Similar sample sizes were observed for ischemic stroke cohort (N at 6 months of NOAC use- 3289, 9 months-2395 and 12 months- 1651) and cohort for DVTPE (At 6 months of adherence assessment, N=3416, at 9 months N= 2503 and at 12 months N=1739). According to American College of Chest Physicians (ACCP), 3-6 months of NOAC treatment is prescribed to prevent the

recurrence of DVTPE, hence the cohort to analyze recurrent DVTPE was based on patients who had prior DVTPE and 3 and 6 months of adherence assessment after the start of the treatment (N at 3 months – 4062, 6 months- 3440). Please check Table 2.2 in Tables and Figures for analysis population and sample size for each cohort. Figure 2.1 in Tables and Figures describes the cohort sample selection in detail.

Overall Baseline Characteristics

The mean age of the overall cohort was 65 years with more men (>70%) than females. The majority of the patients were either from the South or the Midwest (54%). Most of the patients used (>60%) 'Point of service' as their health insurance type. The proportion of patients (60% vs. 40%) with moderate-high risk (based on CHA_2DS_2VASC score > 2) was higher compared to the low-risk (1-2) patients. Most (>82%) of the patients had at least 1 comorbidity. The statins (>60%) and ace-arb inhibitor use (>51%) were most commonly used as other medication in the pre-index period. Please refer to Table 2.2 in Tables and Figures II for details on demographic characteristics.

Adherence measured by PDC

Adherence was measured at 6, 9 and 12 months in the adherence assessment period as described in the METHODOLOGY section. Patients were termed adherent based on PDC ≥80%. The proportion of adherent patients for bleeding cohort at 6, 9, 12 months was 82.7%, 76.2%, 77.9% respectively. A similar proportion of adherence was observed for ischemic stroke (82.6%, 76.2%, 78.3%) and DVTPE (82.7%, 76.4%, 78.4%) cohorts at 6, 9, 12 months. Overall, the adherence to NOACs decreased over a period of 9

months and stabilized over the final 12-month assessment. Please refer to Table 2.1 in Tables and Figures II for adherence estimates.

Matched Cohorts

First, the propensity score matching was performed using a caliper matching of 0.2 and "without replacement" which led to very low sample size due to fewer controls (high adherence). Propensity score matching was tried using caliper matching of 0.2 and "with replacement" of controls. A higher proportion of adherence (>70%) led to multiple pseudo-matching controls with poorly matched cohorts. To remove the bias with minimal loss of patients, IPTW method was used to match the patients based on the propensity score. The covariates used in the propensity score model (Age, gender, insurance, region, CHAD2VASC score, CCI, cardiac drug use – Appendix Table 2) were compared between the matched adherent and non-adherent cohorts. Based on the non-significant p-values (>0.1), IPTW provided better matching with marginal effect on the sample size. Further results are presented and interpreted based on IPTW cohorts. Please See Table 2.2 in Tables and Figures II to compare matched cohorts between caliper and IPTW techniques.

Bleeding Risk and Adherence

The overall incidence of bleeding in the cohort was 5.91% and 4.21% based on 6 and 12-month adherence assessment. The proportion of bleeding after 6 months of adherence assessment was slightly higher in adherent patients compared to non-adherent patients (6.34 vs. 5.29 p=0.165), but the association was not statistically significant. Similarly,

after long-term use (12 months), adherent patients were more likely (4.41 vs. 3.99 p=0.676) to have an occurrence of bleeding as compared to the adherent patients, but the association was non-significant. On an average, the total follow-up time for outcome evaluation was 8.8 months after 6 months of adherence assessment and 6.7 months after 12 months of adherence assessment. Please see Table 2.3 in Tables and Figures II for frequencies and relative risks based on IPTW matched data.

The association was further examined using multivariate Cox proportion hazards models (to control for the variable time) and GLM models adjusted by the IPTW weights. Based on the multivariate Cox model, at the end of 12-month usage, non-adherent patients were marginally less likely to experience a major bleeding [HR=0.940 (0.583-1.515 p=0.798)] compared to the adherent patients. A similar result was obtained using Poisson model (RR=0.905 p=0.683) for non-adherence, which led to the fewer bleeding events, but the relationship was not statistically significant (Please see Table 2.5 in Tables and Figures II). This trend was also consistent for short-term (6-month) use all three models (Cox and GLM- Please see Table 2.4/2.5 in Tables and Figures II). Overall, the adherence was modestly associated with elevated bleeding but was not significantly different between adherent and non-adherent patients. Hence, higher adherence in NOACs might not significantly increase the risk of bleeding.

Risk of Ischemic Stroke and Adherence

The incidence of ischemic stroke was 3.11% based on the adherence assessment period of 12 months. The proportion of ischemic stroke were lower among adherent patients at 6, 9, and 12 months (2.63 vs. 4.39; 2.62 vs. 3.96; 2.19 vs. 4.12) respectively, a significant

association between adherence and stroke risk was observed at 6 and 12 months of adherence assessment. At 6-month drug use, non-adherent patients were 1.66 times (1.1509 – 2.4121) more likely to experience an ischemic stroke compared to the adherent patients. Similarly, non-adherent patient at 12 months were 1.88 times more likely to have an ischemic stroke. The total follow-up period for assessment of ischemic stroke was 9.08 months for patients with 6-month of NOAC use and 6.82 months for 12-month drug use. Please see Table 2.3 in the Tables and Figures II for frequencies and relative risks based on IPTW.

A Cox proportional hazards model for risk of ischemic stroke after 6 and 12-month of drug use was high among non-adherent patients with a hazards ratio of 1.71 (CI-1.178-2.501, p=0.0049) and 1.94 (CI- 1.097-3.427, p=0.0226).

Both GLM and Cox models for 9 and 12-month showed a similar trend (higher risk of stroke among non-adherent patients) with non-significant estimates. (Please see Table 2.4/2.5 in Tables and Figures II). Based on 6 and 12-month adherence assessment, non-adherence to NOAC treatment was significantly associated with elevated risk [RR=1.6661, p=0.0078 and RR=1.8813, p=0.0295 respectively] of ischemic stroke risk compared to the adherent patients. (Please see Table 2.5 in Tables and Figures II). Overall, adherence to NOACs is protective for an incidence of ischemic stroke over the short-term while providing less significant effect over a long-term drug use.

Risk of DVTPE and Adherence

At 12 months, the incidence of DVTPE was 1.11%. The follow-up time for outcomes post 6 and 9-month adherence assessment was 9.08 months and 6.82 months.

The incidence estimates for DVTPE were higher among non-adherent compared to adherent patients based on 6 (1.04% vs 2.71%), 9 (0.44 vs. 2.36%), and 12-month (0.43% vs. 1.84%) adherence respectively. Please see Table 2.3 in Tables and Figures II.

Based on multivariate results using the Cox model, non-adherence had a significant [HR – 2.703 (1.572-4.646)] association with risk DVTPE based on 6 months of NOAC usage. Patients who were non-adherent based on 12-month assessment had a higher risk [HR - 4.603 (1.508-14.053)] of DVTPE compared to the non-adherent patients. (Table 2.5 in Tables and Figures II).

Using the Poisson model, the adjusted estimated hazard of DVTPE in non-adherent patients were significantly higher (RR – 2.603, 5.316, 4.287) based on 6, 9 12-month adherence compared to the adherent patients which corroborated the results based on the Cox models. The high hazard ratios and risk estimates from the GLM models can be attributed to very few numbers of patients with outcomes in this cohort with 12 months of drug use. (Please see Tables 2.4/2.5 Tables and Figures II for multivariate results).

Risk of recurrent DVTPE and Adherence

Although the incidence of recurrent DVTPE was very low (0.87% at 3 months' drug use and 0.55% for 6 months' drug usage), adherence was significantly associated with the reduction of recurrent DVTPE in patients who already had a pre-index occurrence. This association was observed for both 3-month and 6-month adherence to NOACs (incidence of recurrent DVTPE for adherence vs. non-adherence: 0.35 vs. 1.53 at 3 months and 0.08 vs. 1.08 at 6 months) respectively, where non-adherence increased the risk of DVTPE.

Based on a multivariate Cox model, non-adherence was significantly associated with increased risk of recurrent DVTPE [HR=6.178 (1.845 -20.682)] after 6 months of treatment. (Table 2.5 Tables and Figures II). Poisson model suggested higher risk (HR – 4.342 p=0.0003) of recurrent stroke in non-adherent patients based on 6-month adherence. The adherence to the NOAC therapy provides a clear trend of secondary preventive effect for recurrent DVTPE over a period of 3-6 months after the therapy, although the low incidence of outcomes in the study might be responsible for the inflated estimates.

Model Testing

Overall, the model fit examined with the help of deviance for GLM models using Poisson distribution was good with Pearson's chi-square <1 (no re-scaling using adjusting of Pearson's or deviance residual was required). Schoenfeld residuals to assess the proportionality of hazard were mostly parallel for hazards over time for adherence as a covariate. The models were also tested by adding an interaction term for adherence and follow-up time to evaluate the effect; non-significant estimates on the interaction term helped confirm the assumption of proportional hazards. The GLM models using negative binomial distribution mostly converged except models for recurrent DVTPE at 3 and 6 months of therapy.

DISCUSSION

Based on large real-world cohort, our results indicate that there is a significant association of adherence to NOAC therapy and a reduction in ischemic strokes and DVTPE at 6 and 12 months and recurrent DVTPE after 3 and 6 months of NOAC treatment. Furthermore, based on our results, higher adherence might not lead to significant increase in bleeding events.

The adherence to NOACs in our study was greater than 70%, which is consistent with the literature [48,49]. The overall follow-up to assess outcomes was more than 8.5 months and 6.5 months for a 6-month and 12-month adherence assessment (exposure) period respectively, for the NOAC drugs. This will be the first study to examine the impact of adherence on outcomes such as major bleeding, ischemic stroke, DVTPE and recurrent DVTPE using propensity score-matched cohorts. Since the NOACs have already shown better efficacy results against warfarin, evidence that adherence is more beneficial to reduce the outcomes may lead to even greater cost savings. Our study not only concurs with the previous findings in hypertensive drug classes that better adherence to the drug leads to reduced stroke risk and other cardiac-related events but also translates the evidence to NOACs (anticoagulants).[25,50]

Overall, we found a higher incidence of ischemic stroke and bleeding in our real -world study as compared to the estimates found in the clinical trials. It was noteworthy that the number of bleeding events was not significantly different between adherence cohorts for the short and long-term use of NOACs. Our estimates of major bleeding were comparable to (4.21%) to previous studies which reported the occurrence of major bleeding in patients taking NOACs [51]. In a study by Mercaldi et.al on 2 million patients

from Centers for Medicare and Medicaid Services, the rate of ischemic stroke was 3.9 per 100 patient-years, and major bleeding 7.58 per 100 patient-years based on a follow-up of approximately 2 years [52]. In a study based on 2010-2011 data for Medicare beneficiaries, the incidence of major bleeding was higher in dabigatran vs. warfarin (9% vs.5.9%).[53] In a recent study based on 64,661 AF patients in the OPTUM database, the overall incidence of major bleeding was 3.7 per 100 person-years which seemed consistent with our estimates.[54]

Our study reported an incidence of 3.11% for stroke at 12 months of adherence. In another retrospective study on 2006-2008 Medicare beneficiaries, the stroke rate of patients with AF was 3.3% which is consistent with our estimate.[55] A study using Medicare population (N= 134 414) reported fewer stroke rates in dabigatran as compared to warfarin (1.12 vs. 1.34 per100 person-years).[56] The stroke rates for dabigatran using a Medicare claims database (N= 64 935) was 1.73 per 100 person-years.[57] The slightly higher incidence of stroke in our study may be due to a higher proportion of patients with moderate-high risk of stroke (60%) in the overall population.

A study based on combined data from MarketScan and OPTUM reported the incidence rate of DVTPE as 0.58.[58] The incidence of recurrent DVTPE in our study ranged from 0.55-0.87 over 3 and 6 months of NOAC use.

We used large claims data since our hypothesis and study designed required to have a large sample. To address the selection bias and residual confounding, the adherence based cohorts were matched based on stroke risk ($CHAD_2SVAS_2C$) and other covariates including CCI, age, gender, insurance, region, prior cardiac drug use. The issue in regards to the multiple pseudo-controls due to less control as compared to cases was addressed

using IPTW, which helped to achieve better matching. The study design helped to achieve a sequential order of exposure preceding the outcome, but this led to an exclusion of outcomes occurring between index and end of adherence assessment. Furthermore, adherence assessment based on 3, 6, 9, and 12-month windows might lead to truncation of the data. Therefore, the windows were kept close at every 3 months. ICD-9 codes were selected based on an in-depth literature survey where only those reported to have a value of ≥ 90 Positive Predictive Value (specificity and sensitivity) were included. This criterion helped us to have a better confidence in the selection of patients and avoid misclassification. Sensitivity analysis using the Poisson model helped to validate the results over a short and long term (6, 9, 12-months). Recently in Feb 2016, a manuscript was published based on the study, which examined an effect of adherence on stroke. The adherence estimated with PDC was low (47%) which can be attributed to longer follow-up time as compared to our study. Furthermore, the study found adherence is protective of stroke risk at 3, 6, and >6 months which agrees with our results.[54] Our study is unique in a way where the outcomes, including stroke, bleeding and DVTPE are compared between propensity-matched adherence based cohort which controls for the selection bias. Also, our study will be the first to understand the effect of adherence on DVTPE and recurrent DVTPE.

It should be acknowledged that OPTUM is mostly a commercial database under-represented by Medicare population (above 65 years). Over 65% of the sample was represented by males, predominantly from the South or the Midwest and the database lacked information in regards to the race, ethnicity and reason for discontinuation of therapy.

Although in the analysis, clinical variables (e.g. INR values, left ventricular ejection fraction, body mass index) were not included, clinical markers of severity such as CHA_2DS_2VASC and CCI helped to control for risk due to hypertension, prior cardiovascular disease, diabetes and other co-morbidities. Prior use of cardiac drugs was also accounted. However, aspirin use was not comprehensively captured in the claims database due to availability as an Over the Counter (OTC) drug. Since the study period for this analysis was from 2010-2012, a limited follow-up time was achievable for outcomes to occur. Moreover, the newer drugs apaxiban and edoxaban came into the market after 2012 were not included. Despite these limitations, the study provides valuable evidence in regards to adherence to NOACs and its short and long-term effects on bleeding, ischemic stroke and recurrent DVTPE controlling for other factors.

CONCLUSION

Adherence to NOACs is suboptimal for anticoagulation control and decreases over time. Overall, adherent NOAC patients had lower rates of ischemic stroke, DVTPE, and recurrent DVTPE compared to non-adherent patients. Short and long term risk of bleeding was not significantly different between adherent and non-adherent patients. The short and long-term estimates of adherence to NOACs and its effect on the risk of bleeding, stroke, and DVTPE as observed in our study may help the healthcare providers and managed care organizations to compare risk-benefits of prescribing NOACs. The findings will further help to provide optimal care to patients by improving adherence and reduce HCRU and healthcare costs. Future research on adherence to NOACs including the newer drugs and longer follow-up times is warranted.

TABLES AND FIGURES II

Figure 2.2: Cohort Selection Based on Inclusion and Exclusion Criteria

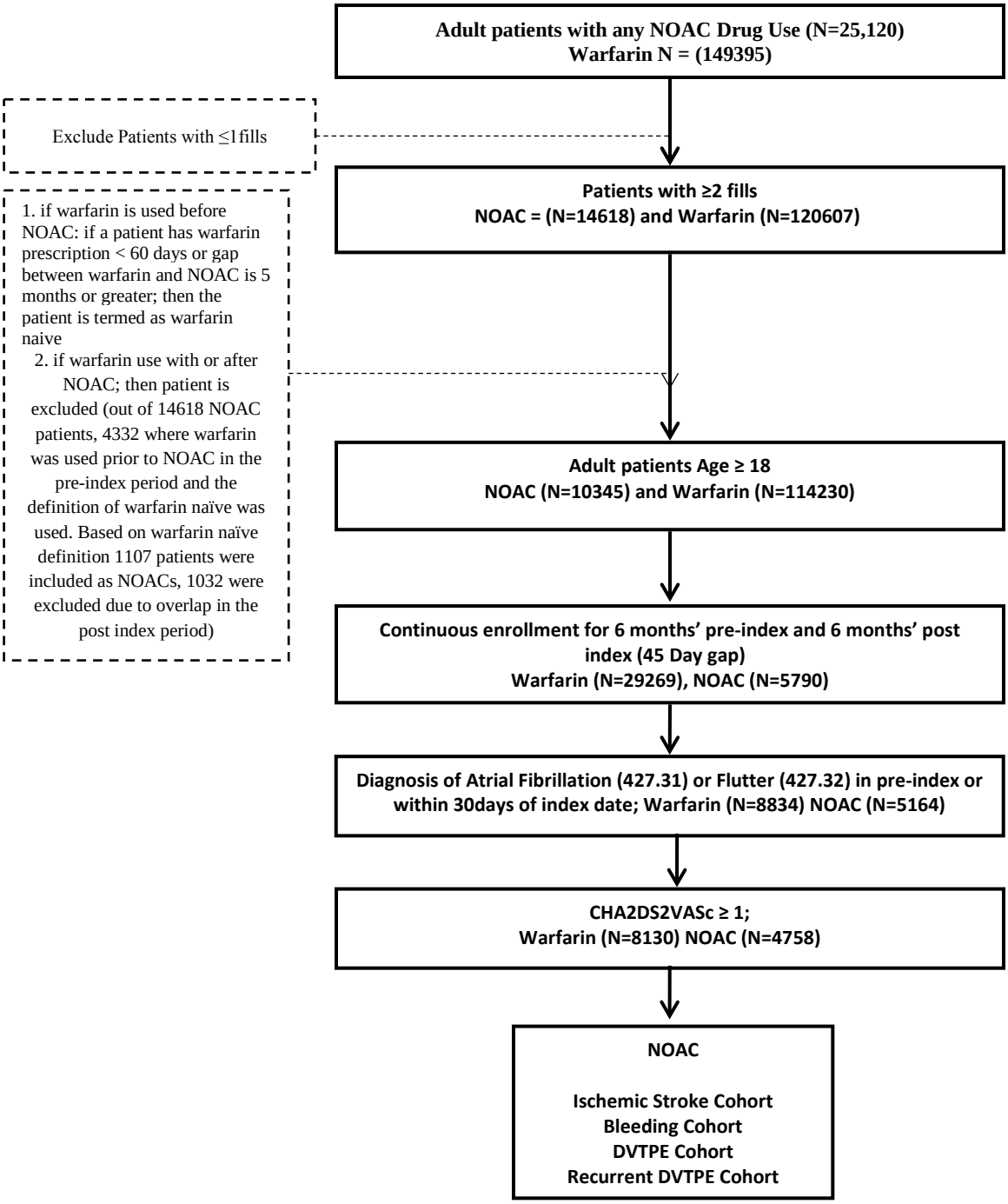


Table 2.1: Adherence for Cohorts at Varying Time-points

Outcome cohort	Time point	Category	N	% Adherence
Bleeding (n=3285)	6 months	Non-Adherent	569	17.32
		Adherent	2716	82.68
Bleeding (N=2353)	9 months	Non-Adherent	561	23.84
		Adherent	1792	76.16
Bleeding (N=1617)	12 months	Non-Adherent	357	22.08
		Adherent	1260	77.92
Ischemic Stroke (N=3289)	6 months	Non-Adherent	573	17.42
		Adherent	2716	82.58
Ischemic Stroke (N=2395)	9 months	Non-Adherent	571	23.84
		Adherent	1824	76.16
Ischemic Stroke (N=1651)	12 months	Non-Adherent	359	21.74
		Adherent	1292	78.26
Recurrent DVTPE (N=4062)	3 months	Non-Adherent	638	15.71
		Adherent	3424	84.29
Recurrent DVTPE (N=3440)	6 months	Non-Adherent	592	17.21
		Adherent	2848	82.79
DVTPE (N=3416)	6 months	Non-Adherent	588	17.21
		Adherent	2848	82.79
DVTPE (N=2503)	9 months	Non-Adherent	590	23.57
		Adherent	1913	76.43
DVTPE (N=1739)	12 months	Non-Adherent	375	21.56
		Adherent	1364	78.44

Table 2.2: Comparison of Propensity Matched Cohort by Caliper and IPTW

		Caliper Matching				IPTW			
Variable Description	Statistic Response Category	Total (N= 2,520)	Adherent (N= 1,260)	Non-Adherent (N= 1,260)	P-value (Chi-sq)	Total (N= 1,617)	Adherent (N= 1,260)	Non-Adherent (N= 357)	P-value (Chi-sq)
Age at index	N	2520	1,260	1,260	<0.3029	1617	1,260	353	0.6601
	Mean (SD)	65.84 (10.65)	65.62(10.05)	66.06 (11.21)		64.83 (10.45)	64.89 (8.15)	64.6 (16.93)	
	Median(IQR)	64(58,73)	64 (59,73)	64 (57,72)		63 (58,72)	63 (59,72)	63 (57,72)	
	Range	34,86	34,86	34,86		26,86	34,86	26,86	
Gender	Female	839 (33.29)	380 (30.16)	459 (36.43)	<0.001	491 (30.46)	252 (30.48)	240 (30.44)	0.9865
	Male	1,681 (66.71)	880 (69.84)	801 (63.57)		1,122 (69.54)	574 (69.52)	548 (69.56)	
Insurance type	EPO	261 (10.36)	134 (10.63)	127 (10.08)	<0.001	192 (11.88)	96 (11.69)	95 (12.09)	0.4507
	HMO	100 (3.97)	69 (5.48)	31 (2.46)		101 (6.28)	50 (6.08)	51 (6.50)	
	IND	450 (17.86)	200 (15.87)	250 (19.84)		230 (14.24)	121 (14.62)	109 (13.84)	
	POS	1,550 (61.51)	790 (62.70)	760 (60.32)		1,029 (63.78)	520 (62.95)	509 (64.65)	
	PPO	159 (6.31)	67 (5.32)	92 (7.30)		62 (3.82)	38 (4.66)	23 (2.93)	
Region	Midwest	530 (21.03)	286 (22.70)	244 (19.37)	0.0001	327 (20.25)	177 (21.41)	150 (19.04)	0.5577
	Northeast	274 (10.87)	124 (9.84)	150 (11.90)		152 (9.40)	81 (9.81)	71 (8.97)	
	South	1,181 (46.87)	635 (50.40)	546 (43.33)		863 (53.52)	430 (52.13)	433 (54.97)	
	West	535 (21.23)	215 (17.06)	320 (25.40)		272 (16.83)	137 (16.65)	134 (17.02)	
CHA2D2VASC Score	Low risk	977 (38.77)	483 (38.33)	494 (39.21)	0.6529	653 (40.51)	332 (40.21)	322 (40.83)	0.8014
	Mod-high risk	1,543 (61.23)	777 (61.67)	766 (60.79)		960 (59.49)	493 (59.79)	466 (59.17)	
CCI category	CCI score 0	484 (19.21)	226 (17.94)	258 (20.48)	0.0024	290 (17.99)	151 (18.26)	140 (17.72)	0.8298
	CCI score 1-2	1,171 (46.47)	629 (49.92)	542 (43.02)		789 (48.91)	407 (49.34)	382 (48.46)	

	CCI score 3 and+	865 (34.33)	405 (32.14)	460 (36.51)		534 (33.10)	267 (32.40)	266 (33.82)	
Statin use	No	1,068 (44.46)	513 (40.71)	555 (44.05)	0.0846	787 (48.76)	396 (47.96)	391 (49.61)	0.5078
	Yes	1,334 (55.54)	688 (54.60)	646 (51.27)		826 (51.24)	430 (52.04)	397 (50.39)	
ACE ARB inhibitor	No	1,159 (48.25)	567 (45.00)	592 (46.98)	0.3073	835 (51.79)	420 (50.83)	416 (52.79)	0.4293
	Yes	1,243 (51.75)	634 (50.32)	609 (48.33)		778 (48.21)	406 (49.17)	372 (47.21)	
Beta-blocker use	No	1,685 (70.15)	836 (66.35)	849 (67.38)	0.5621	1,145 (70.98)	582 (70.55)	563 (71.43)	0.6962
	Yes	717 (29.85)	365 (28.97)	352 (27.94)		468 (29.02)	243 (29.45)	225 (28.57)	

CCI- Charlson's comorbidity Index, HMO – Health maintenance organization, PPO- Preferred provider organization, EPO - Exclusive provider organizations, IND- Independent, POS-Point of service, ARB- Angiotensin Receptor Blocker, ACE- Angiotensin-converting enzyme

Table 2.3: Incidence Estimates for Outcomes in Propensity (IPTW) based Adherence Groups

Adherence	Mean (SD) Follow up time (months)	N	Major Bleeding	N	Adherent	N	Non-adherent	Relative Risk	Chi-sq p-value
6 months	8.80 (5.31)	3249	192 (5.91)	1746	112 (6.34)	1503	79 (5.29)	0.8214 (0.6216-1.0855)	0.1657
9 months	7.74 (4.49)	2348	122 (5.27)	1195	63 (5.54)	1153	59 (4.99)	0.9653 (0.6832- 1.3639)	0.8414
12 months	6.67 (3.63)	1613	68 (4.21)	825	36 (4.41)	788	32 (3.99)	0.90935 (0.5675-1.443)	0.6764
Adherence		N	Ischemic Stroke	N	Adherent	N	Non-adherent	Relative Risk	Chi-sq p-value
6 months	9.08 (5.31)	3252	112 (3.44)	1755	46 (2.63)	1496	66 (4.39)	1.6661 (1.1509-2.4121)	0.0062
9 months	7.91 (4.53)	2389	78 (3.28)	1218	31 (2.62)	1171	46 (3.96)	1.5128 (0.9709 –2.3573)	0.0652
12 months	6.82 (3.64)	1641	51 (3.11)	856	19 (2.19)	785	32 (4.12)	1.8812 (1.0737-3.2966)	0.0246
Adherence		N	Recurrent DVTPE	N	Adherent	N	Non-adherent	Relative Risk	Chi-sq p-value
3 months	11.64 (5.48)	3995	35 (0.87)	2234	8 (0.35)	1761	26 (1.53)	4.34 (1.9656-9.5956)	0.0001
6 months	9.22 (5.32)	3394	18 (0.55)	1851	3 (0.08)	1543	15 (1.01)	5.892 (1.7638-19.6866)	0.0010
Adherence		N	DVTPE	N	Adherent	N	Non-adherent	Relative Risk	Chi-sq p-value

6 months	9.15 (5.32)	3372	51 (1.68)	1836	19 (1.04)	1536	42 (2.71)	2.6035 (1.5212-4.4555)	0.0003
9 months	7.97 (4.51)	2497	35 (1.38%)	1272	6 (0.44)	1224	29 (2.36)	5.3167 (2.1656 -13.052)	<.0001
12 months	6.85 (3.64)	1730	19 (1.11%)	898	4 (0.43)	832	15 (1.84)	4.2873 (1.4105-13.0314)	0.0050

Table 2.4. Cox Model for Association of Adherence with Bleeding using the IPTW Matched Data

	Independent Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits		Pr > Chi Sq
Bleeding at 6 months	Adherence vs Non Adherence	0.844	0.633	1.125	0.2478
Bleeding at 9 months	Adherence vs Non Adherence	0.989	0.694	1.411	0.9527
Bleeding at 12 months	Adherence vs Non Adherence	0.940	0.583	1.515	0.7982
Stroke at 6 months	Adherence vs Non Adherence	1.716	1.178	2.501	0.0049
Stroke at 9 months	Adherence vs Non Adherence	1.519	0.968	2.385	0.0690
Stroke at 12 months	Adherence vs Non Adherence	1.939	1.097	3.427	0.0226
Recurrent DVTPE at 3 months	Adherence vs Non Adherence	4.568	2.062	10.122	0.0002
Recurrent DVTPE at 6 months	Adherence vs Non Adherence	6.178	1.845	20.682	0.0031
DVTPE at 6 months	Adherence vs Non Adherence	2.703	1.572	4.646	0.0003
DVTPE at 9 months	Adherence vs Non Adherence	5.531	2.245	13.627	0.0002
DVTPE at 12 months	Adherence vs Non Adherence	4.603	1.508	14.053	0.0073

Table 2.5. Poisson and Negative Binomial Model Results for Association of Adherence with Bleeding using the IPTW Matched Data

		Poisson				Negative Binomial			
	Independent Variable	Estimate	Confidence Limits		Pr > Chi Sq	Estimate	Confidence Limits		Pr > Chi Sq
Bleeding at 6 months	Adherence vs Non Adherence	0.8214	0.6164	1.0947	0.1794	0.8016	0.5381	1.1940	0.2766
Bleeding at 9 months	Adherence vs Non Adherence	0.9653	0.6769	1.3767	0.8455	0.8639	0.5604	1.3318	0.5077
Bleeding at 12 months	Adherence vs Non Adherence	0.9053	0.5618	1.4590	0.6830	0.8141	0.4457	1.4869	0.5033
Stroke at 6 months	Adherence vs Non Adherence	1.6661	1.1436	2.4275	0.0078	1.5965	0.9992	2.5510	0.0504
Stroke at 9 months	Adherence vs Non Adherence	1.5128	0.9639	2.3743	0.0718	**			
Stroke at 12 months	Adherence vs Non Adherence	1.8813	1.0648	3.3241	0.0295	1.5319	0.7817	3.0019	0.02140
Recurrent DVTPE at 3 months	Adherence vs Non Adherence	4.3429	1.9608	9.6192	0.0003	**			
Recurrent DVTPE at 6 months	Adherence vs Non Adherence	5.8926	1.7604	19.7238	0.0040	**			
DVTPE at 6 months	Adherence vs Non Adherence	2.6034	1.5148	4.4745	0.0005	2.4260	1.2864	4.5750	0.0062
DVTPE at 9 months	Adherence vs Non Adherence	5.3167	2.1582	13.0976	0.0003	**			
DVTPE at 12 months	Adherence vs Non Adherence	4.2873	1.4049	13.0835	0.0106	4.9690	1.7241	14.3210	0.0030

*: The relative Hessian convergence criterion was greater than the limit of 0.0001. The convergence is questionable. Negative of Hessian not positive definite

** Algorithm didn't converge

APPENDICES II

Appendix II: Table 1 ICD-9 Diagnosis codes

		ICD-9 Codes
AF Diagnosis	Atrial Fibrillation and Flutter	427.31, 427.32
	Hypothyroidism	240.9
CHA2DS2VASC Score	Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.x, 518.4
	Diabetes	250.x, 357.2, 362.0, and 366.41
	Hypertension	401.x, 402.x, 403.x, 404.x, and 405.x
	Stroke TIA	433,434, 435, 436
	Vascular disease	410,411,412, 413, 414, 443.8, 443.9
Major Charlson's Comorbidity Index diagnosis	Myocardial Infarction	410, 412
	CHF	428
	Cerebrovascular disease	430-438
	COPD	490-496, 500-505, 506.4
	Paralysis	342, 344.1
	Chronic Renal failure	582, 585, 586, 588, 583.0 – 583.7
	Ulcers	531-534
	Cirrhodites	5712, 5714, 5715, 5716
	AIDs	042,044
	Metastatic tumor	196.0-199.1, 196.x
Major Bleeding	GI	456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x
	Intracranial	430, 431, 432.x, 852.x, 853.x
	Other sites	423.0, 459.0, 596.7, 599.71, 719.1x, 784.8, 786.3
Ischemic Stroke		433.x1, 434.x1, or 436
DVT		45111, 45119, 4512, 45181, 4519, 45340, 45341, 45342, 4538, 4539
PE		4151, 41511, 41519

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Appendix II: Table 2 Variable Information

Variable	Type	Coding
Charlson's Comorbidity Index	Categorical	0=CCI score 0 1=CCI score 1-2 2=CCI score 3 or more
CHASD2SVASC Score	Categorical	1=low risk (1-2) 2=mod-high risk (>2)
Region	Categorical	STATES CT,ME,MA,NH,RI,VT,NJ,NY,PA = Northeast IN,IL,MI,OH,WI,IA,KS,MN,MO,NE,ND,SD = Midwest DE,DC,FL,GA,MD,NC,SC,VA,WV,AL,TN,KY,MS,AR, LA,OK,TX = South AZ,CO,ID,NM,MT,UT,WY,NV,AK,CA,HI,OR,WA = West
Insurance Type	Categorical	EPO=1 HMO=2 IND=3 OTH=4 POS=5 PPO=6
Age	Continuous	NA
Beta blocker Use ARB Use Statin Use Ace Inhibitor Use	Categorical	1= Yes 0=No
Gender	Categorical	1 =Male, 0 =Female

Appendix II: Table 3 Cox Models for Outcomes at Different Time-points

cox model without covariates.rtf

Appendix II: Table 4 Poisson and Negative Binomial Models for Outcomes at Different Time-points

Negbin and Possion without cov

Appendix II: KM graphs for events by adherence

KM.docx

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MANUSCRIPT III

DISTRIBUTION OF COSTS AND HEALTHCARE UTILIZATION FOR OUTCOMES IN PATIENTS USING NOACS (DABIGATRAN & RIVAROXABAN) AND WARFARIN

Formatted for submission to the Journal of Managed Care Pharmacy (JMCP), not yet submitted.

ABSTRACT

Introduction: Novel Oral Anti-coagulants (NOACs including Dabigatran and Rivaroxaban) are new promising drugs which have shown better or similar efficacy to lower stroke risk and fewer side effects compared to warfarin in the clinical trials. In recent studies, Dabigatran and Rivaroxaban have demonstrated to have lower costs than warfarin. Although the estimates are based on numerous simulated economic modeling studies and meta-analysis, there is limited evidence in real world data to explain the distribution of cost and healthcare resource utilization (HCRU) for outcomes in NOACs. This study examined the adjusted AF-related costs (NOAC vs. warfarin) along with its sub-components (inpatient, outpatient, and drug costs) and HCRU. Additionally, bleeding related unadjusted cost was also calculated. Costs were further investigated for subgroups based on age, region, insurance type gender, CHA_2DS_2VASc, CCI. Moreover, a possible relationship between adherence to medication and HCRU/cost was also explored. The evidence is critical as the NOACs move towards competing against warfarin (generic) as an anticoagulant.

Methods: A retrospective cohort study was conducted utilizing data from the Optum® Clinformatics™ Data Mart (Optum Insight, Eden Prairie, MN) database between January 1, 2010 and December 31, 2012. The study population was identified based on documentation of ≥ 1 diagnosis of atrial fibrillation or flutter ICD-9 code 427.31/32, ≥ 2 prescriptions of NOAC or warfarin, age $\geq$18 years and CHA_2DS_2VASC score $\geq$1. The index date was the first prescription claim for NOAC or warfarin. The adjusted HCRU and costs were calculated at 6 months, annually, as well as by per patient per month using

GLM models (gamma distribution) and compared between NOAC and warfarin cohorts. As an exploratory analysis, the HCRU and costs were compared across adherent (>80% PDC) and non-adherent NOAC patients.

Result: Annual drug cost was higher for NOAC users ($4988 vs. $331) was offset by higher medical costs for warfarin users (Total annual cost for warfarin $31,400 vs. $22,134). The mean annual ER visits (14 vs. 13) and office visits (76 vs. 49) for warfarin users was slightly higher compared to NOAC users.

Highest cost drivers for drug cost for warfarin users was patients from Northeast. Conversely, highest cost drivers for medical cost were patients less than <65 years and patients with CCI +3.

For NOACs, the highest cost driver for the drugs was user who were 65 and above, from Northeast, $CHA_2DS_2VAS_C$ >2 (mod-high risk), and independent insurance. Additionally, medical cost was driven by EPO insurance and CCI+3.

Although ER visits (13.78 vs. 14.47), and inpatient costs ($20,756 vs. $23,208) were lower among the adherent patients, there was no significant difference in estimates between adherence and non-adherent patients.

Conclusion: Although drug cost was higher among NOAC users, the total cost was offset by higher cost for warfarin users in inpatient and outpatient setting. The costs presented by subgroups can help to target specific patient groups (higher CCI index, high stroke risk, patients from the Northeast, POS insurance) for greater cost savings. Adherence to NOACs is slightly helpful to reduce costs and HCRU but might not lead to substantial monetary benefits to the patient and the provider.

BACKGROUND

Atrial Fibrillation (AF) is a common condition causing cardiac rhythm disturbance due to electrophysical or structural abnormality resulting in abnormal impulse formation.[1] AF is one of the key risk factors for ischemic stroke, increasing the risk up to 5-fold[2]. In 2010, the prevalence of AF in the United States (US) was 2.7 to 6.1 million and is expected to grow between 5.6 and 12 million in 2050.[3] In the US, AF accounts for a total of >467,000 hospitalizations annually and leads to >99,000 deaths per year. AF is also responsible for adding an amount of $26 billion to the US healthcare spending annually, which is mostly driven by the inpatient and outpatient costs.[1]

Use of NOACs in AF

Treatment options for AF primarily include antiplatelet, anticoagulant, beta blockers, calcium channel blockers, sodium and potassium channel blockers.[4] Anticoagulants significantly decrease symptoms and health outcomes leading to significant patient benefits.[5] Warfarin is an oral vitamin K-antagonist approved in 1954 and has been a gold standard of care for more than 50 years. The variable dosing, frequent dose adjustments and narrow window for therapeutic use in warfarin have prevented its the widespread utilization in patients. Moreover, interactions with concomitant medications, change in the diet, and the need for periodic monitoring has made warfarin use challenging for the clinicians and patients.[6]

NOACs include newly approved oral drugs: dabigatran “Pradaxa” (2010), rivaroxaban “Xarelto” (2011), apaxiban and edoxaban. Overall, NOACs have shown better or similar efficacy compared to warfarin in the clinical trials. Few benefits of NOACs include:

quick time-to-peak effects, fixed dosing regimens, require little monitoring, and have a fewer drug to drug interactions. Although an antidote is now available for dabigatran and its copays have been lowered since the launch of the drug, the total cost of the branded NOACs compared to the generic warfarin is very high. The challenge for the policy decision makers and drug reimbursement is to weigh if the high drug costs for NOAC's offsets the other related medical costs, outcomes and quality of life.

NOACs and Healthcare costs

NOACs have been widely prescribed and covered by the insurance providers and Medicare Part D although the copays may vary from $30-$120.[7] According to a claims database study by Desai et.al on 6893 patients, NOACs accounted for 62% of new prescriptions and 98% of anticoagulant-related drug costs in 2014.[8] In some cases, on the formulary, NOACs may require prior authorization (if less expensive drugs might work better), and be used as "Step therapy" to start with the drug after generic alternative. Most of the providers have placed NOACs as Tier 2 (drugs are designated preferred brand because they have been proven to be effective, be safe, and favorably priced compared to other brand drugs) or 3 (have the highest copay or coinsurance, generally not found cost-effective). But it is important to consider that a significant share of the healthcare cost comes from inpatient and outpatient setting and is crucial to guide decision makers in regards to the right treatment selection.

There are some data published on the Healthcare Resource Utilization (HCRU) and economic outcomes of NOACs as a therapy. In the RELY trial, the hospitalizations for dabigatran were lower compared to warfarin (2311 vs. 2458, $p < 0.003$).[9] A study comparing the HCRU between rivaroxaban and warfarin using a Humana claims

database reported fewer hospitalizations in rivaroxaban users compared to warfarin (AF-related, 2.11 vs. 3.02 days; all-cause, 2.71 vs. 3.87 days).[10]

Furthermore, using the same database, the healthcare costs were comparable to warfarin with mean hospitalization costs for rivaroxaban slightly lower than warfarin (all-cause: $5411 vs. $7427), although pharmacy costs were slightly higher for rivaroxaban $5316 vs. $2620 but were not significantly different.[11] For a study based on the HealthCore data, pharmacy costs per month for dabigatran were higher than the warfarin cohort $455(SD,429) vs. $328(SD, 517) but medical costs were comparable $2,696 (SD, 6,699) vs. $2,893 (SD, 6,819). There was no difference in the adjusted total healthcare costs between the two cohorts (dabigatran vs. warfarin: $2949 vs. $2959)[12]. In an economic analysis by Deitelzweig et.al. 2012 using 10,000 Monte-Carlo iterations, it was demonstrated that 92.6% of the time, the one-year medical cost for dabigatran was less than warfarin. Similarly, 79.8% of the time, the one-year medical cost for rivaroxaban was less than warfarin. The study also examined one-year medical costs of major bleedings (excluding hemorrhagic stroke) with dabigatran and rivaroxaban (+$31 and +$108, respectively) compared with warfarin.[13] Based on the literature review of cost in AF patients, the total annual cost in 2013 ranged from $18,454 to $38,270 while inpatient cost was $7,841 to $22,582 per patient.[14] Another database study by Fonseca et.al, the total cost of patients taking dabigatran and warfarin after propensity score matching was 14,794 vs. $16,826.[15]

Overall based on the recently published literature, the NOACs tend to demonstrate better or comparable economic outcomes than warfarin.

The real-world data regarding cost differences and events rate among NOAC treatment is limited. No published study has examined the differences in cost and HCRU outcomes in detail across the clinical subgroups based a real-world data. Also, comparison of the various component costs across adherence cohorts will help explore and generate a hypothesis in regards to the impact of adherence on clinical outcomes and its related HCRU.

Study Rationale and Justification

Although the cost estimates have been predicted by numerous simulated economic modeling studies and meta-analysis, there is limited real-world evidence to further explain the distribution of the costs and healthcare resource utilization for outcomes in NOACs. This study examined the cost along with its sub-components (inpatient, outpatient, and drug cost) and HCRU across (sub-grouped by) clinical factors like age, gender, CHA_2DS_2VASc, CCI. Furthermore, possible relationship of adherence to inpatient costs and HCRU was explored. This evidence is critical as the NOACs move towards competing against warfarin (generic) as an anticoagulant. Comparison between subgroups will help identify the cost drivers and recognize the difference in regards to costs in the real world to help generate hypothesis for in-depth analysis which can target specific subgroup and lead to higher cost savings. The results regarding cost will help understand the landscape and the economic burden of NOACs on the healthcare system. Several inputs from the results can be used for detailed cost-effectiveness analysis and other economic modeling studies.

The proposed study aims to test the following hypothesis

Hypothesis: Ho = There is no statistical difference in cost and HCRU between AF patients taking NOAC and warfarin.

Other analyses focusing in the subgroups and comparison of cost and HCRU between adherent vs. non-adherent patients are aimed to generate a hypothesis.

METHODOLOGY

Study Design

This is a retrospective cohort study design to compare costs and HCRU between NOAC vs. warfarin patients across different subgroups.

The study was conducted using medical and pharmacy claims data from January 1, 2010, to December 31, 2012, using a large-scale US managed care health plan affiliated to Optum® Clinformatics™ Data Mart (Optum Insight, Eden Prairie, MN) database. The primary outcome of the data was adjusted inpatient, outpatient, drug cost and HCRU (inpatient, ER and outpatient visits).

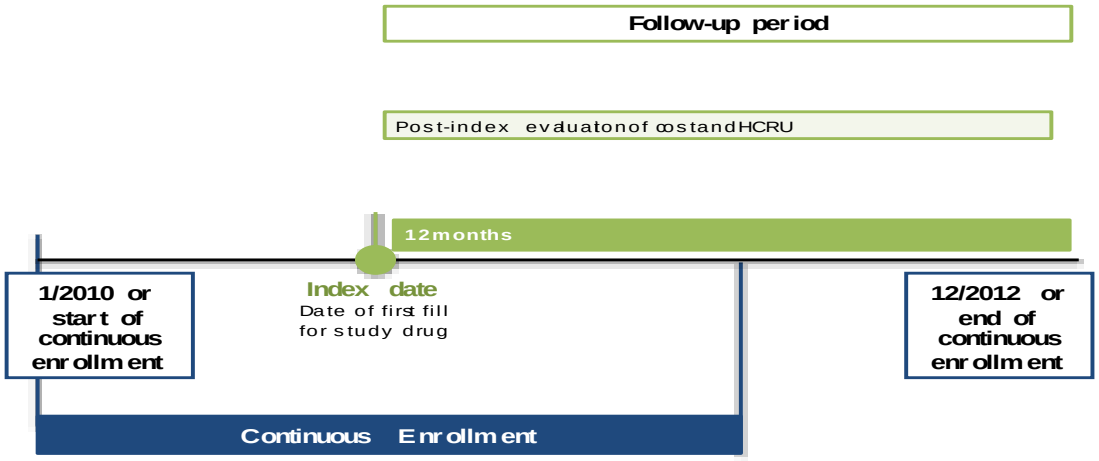
Data source: The OPTUM database mainly includes medical claims, including inpatients and outpatient files and pharmacy claim data. It contains details on dates of service, place of service, International Classification of Diseases, Ninth Revision, Clinical Modification ICD-9-CM/ICD-10 diagnosis codes, provider type, National Drug Code-NDCs, drug quantity dispensed, days supplied, charges, deductibles, and copayments. The large US health plan database includes 14 million patients and 500,000 Medicare enrollees. The member file constitutes the demographic data and eligibility information. The database comprehensively covers diverse geographical areas of US with most of its enrollees from the South and the Midwest. The data access was compliant with the

Health Insurance Portability and Accountability Act. To ensure the patient's confidentiality, no identifiable protected health information was used or analyzed during the study[16] The data was accessed using the server at the University of Rhode Island (URI) and analyzed using SAS EG 7.1. The study was also approved by the Institutional Review Board at URI.

Sampling design/procedures: All patients between January 1, 2010, to December 31, 2012, were identified. Patients with warfarin, dabigatran or rivaroxaban (NOACs) were characterized using the NDC codes and brand name using REDBOOK. The index date was defined as the date of first prescription fill of the NOAC or warfarin in their respective drug cohort. Patients with at least two claims for the study drugs in the post-index period were included. Patients were included based on at least one AF or atrial flutter diagnosis claim identified using the medical file (inpatient or outpatient) with an ICD-9 code of 427.31/427.32 during the pre-index period or 30 days within the index date. In addition to the AF patients, subjects with atrial flutter were also included since a large proportion of patients with atrial flutter also suffer from atrial fibrillation (overlap) and the recommended treatment is similar for AF and flutter in terms of prevention of stroke. Patients with age $\geq$ 18 years were included. Patients with concomitant use of warfarin and NOAC during the post-index assessment period were excluded. Few patients previously used warfarin in the pre-index period prior to starting the NOACs. Since, NOACs are also prescribed to fulfill the unmet need in few patients with prior warfarin use, to avoid exclusion of any NOAC user (and sample size considerations), the inclusion of these patients was based on the definition of "warfarin-naïve." Based on the definition of 'warfarin naïve' in RELY trials, a patient was defined 'warfarin-naïve' if

there was no use of warfarin 2 months before the index date (first fill) of NOACs or if the NOAC was used for a duration of at least 5 or more.[17] This criterion was to ensure we capture all NOAC users and avoid any potential bias in regards to prior warfarin therapy for assessment of outcomes. Thus, the index date of these "warfarin-naïve" users was based on the first prescription fill of NOACs. Data based on RELY trials has shown no heterogeneity between patients who have prior warfarin use (based on the above definition) and those with no prior warfarin therapy. Age was used as a continuous variable. Furthermore, patients with CHA_2DS_2VASC score ≥ 1 (1-9) were identified using ICD-9 codes and included. The CHA_2DS_2VASC characterizes the risk of stroke based on a score composed of (congestive heart failure, hypertension, age >75 years, diabetes, prior stroke, pulmonary or vascular disease, age [65-74 years], sex [as female]). Please refer to Appendix Table 1 for ICD-9 codes. The patients with at least 6 months of pre and post index continuous eligibility with a permissible gap of 45 days were included in the cohort. Patients with hyperthyroidism (ICD-9 242.9) were excluded from the patient cohort since it may be the probable cause AF but is not related to cardiac pathways.

Figure 3.1: Study Design and Timeline



Outcomes

Post-index cost and HCRU was calculated. The medical cost was defined as the total cost of inpatient and outpatient medical services. The medical cost was also inclusive of professional fees and laboratory testing (e.g. prothrombin time, INR monitoring for warfarin). The total healthcare cost was the sum of all medical (inpatient, outpatient) and drug costs. The cost measures were expressed as annual and cost-per-patient per-month was calculated.

HCRU assessment consisted of inpatient visits, outpatient office visits, and ER visits. The cost for the years 2010-2012 was adjusted for inflation to 2016 dollars based on the latest consumer price index (CPI) data by the US government (http://www.bls.gov/data/inflation_calculator.htm). Patients were categorized as adherent (>80%) and non-adherent based on PDC calculated between the index date and 3/6 months and HCRU was evaluated over the post index 1-year follow-up period.

Data Analysis: The data were analyzed using SAS EG version 7.1. The generalized linear models with gamma distribution were used to obtain and compare the adjusted annual and monthly per-patient costs between warfarin and NOAC users. Age, CCI, CHA_2D_2VASC, region, insurance type, gender, and cardiac medication use were used as covariates. The total cost along its sub-components and HCRU was compared between the NOAC vs. warfarin patients at a significance level of $p \leq 0.05$.

The univariate statistics were presented for the subgroup analysis. The mean AF-related and bleeding related costs (all-cause, inpatient, medical, drug) and HCRU for NOAC vs. warfarin users across subgroups were measured. As an exploratory analysis, unadjusted HCRU and costs were compared between patients who were adherent vs. non-adherent.

RESULTS

We found a total of 25,120 users of NOACs and 149,359 users of warfarin within the study period. A total of 14,618 NOAC and 120,607 warfarin users had 2 or more prescription fills. Out of 14618 NOAC patients, 4332 patients had a prior warfarin use in the pre-index period, and the definition of 'warfarin naïve' was used to screen the patients. Based on the definition of 'warfarin naïve', 1107 out of 4332 patients were included as NOACs. A total of 1032 patients were excluded due to an overlap (concomitant use of warfarin and NOACs) in the post-index period. Based on the other inclusion criteria (diagnosis of atrial fibrillation in pre-index period or 30 days within the index date, ≥18 years, continuous enrollment for 6 months pre and post-index, and CHA2DS2VASc ≥1), a total number of warfarin and NOAC patients were 8130 and 4758 respectively.

Based on 6 months of drug use, a total number of 3,453 NOAC users and 5596 warfarin users were included in the analysis. At 12 months of the assessment period (drug use), the study sample consisted of 5057 patients. A total of 1770 NOAC patients and 3287 warfarin patients met the inclusion and exclusion criteria. Figure 1 in Appendix III describes the cohort sample selection in detail.

Baseline Characteristics among NOAC and Warfarin patients

Based on the study sample of 5057 patients, the mean age of the sample was 66 years with more men (66.7%) than females. The majority of the patients were either from the South or the Midwest (65%). Most of the patients (65%) were categorized as moderate to high-risk of stroke based on CHA_2DS_2VASC score >2. Over 80% of patients in the cohort had a CCI above 0. For medication use, statins were the most frequently used drugs (50% of patients) followed by ACE-ARB inhibitors used by more than 25% of the sample.

Based on the chi-square test, most of the patient characteristics were different across the NOACs and warfarin. The females preferred to use NOACs compared to patients using warfarin (69% vs. 64%). More than 50% of NOAC users were from the South (vs. 37% for warfarin users). For the stroke risk based on the CHA_2DS_2VASC score, a higher proportion of warfarin users had a moderate-high risk (more severe) compared to NOAC users (67% vs. 60%). Most of the patients had CCI score > 1(85%) where patients on warfarin therapy were slightly severe (with a higher proportion of 3+ comorbidities) compared to the NOAC users (48% vs. 34%). The statin use was high in both cohorts (>50% of the patients). Please refer to Table 3.1 in Tables and Figures III.

Adherence measured by PDC

Adherence was measured at 3, 6, 9 and 12 months post the index date. Overall, NOAC patients had a higher adherence (PDC ≥80%) to the treatment as compared to the warfarin therapy. At 12 months of follow-up, the proportion of adherent patients using NOAC was 78.42% (N=1388/1770) compared to 61.88% (N=2034/3287) for warfarin patients. The trend for higher adherence in NOACs vs. warfarin was preserved for 3, 6, 9-month assessment period. Table 1.2 in Tables and Figures I compare the adherence measured at different time points between NOAC and warfarin cohorts. The proportion of adherence among NOAC patients at 3 months was (N=2859/3453) 84.30% and declined over time (82.80% for 6 months and 76.45% 9 months). Similarly, the proportion of adherence among warfarin users at 3 months was 77.43% (N=5224/6747) followed by 72.61% and 61.88% for at 6 and 9 months respectively.

Baseline Characteristics among Adherent and Non-Adherent NOAC patients

Based on the 12-months drug usage, the patient demographic and clinical characteristics were summarized for 1388 adherent and 382 non-adherent patients at baseline (index date). Age, CHA_2DS_2VASC score, type of insurance, monthly drug costs and use of statins were different across the adherent and non-adherent patients. The mean age of patients was 65 years with adherent (66 years) patients being older than the non-adherent (62 years) patients. The cohorts consisted of more men (69.3%) than women (30.7%). The majority of patients were from the South (51.3%) or the Midwest (21.9%), and more than 60% of the final cohort received point-of-service (POS) insurance. There were 39.4% patients with a CHA_2DS_2VASC score of 1-2 and 38.8% with a CHA_2DS_2VASC score > 2 (termed as moderate risk). Patients with moderate-high risk of stroke (based on the CHA_2DS_2VASC score) were more adherent compared to the low-

risk patients. The CCI scores were well distributed across adherent and non-adherent patients. In regards to the cardiac medication use, statin and beta-blocker use was higher among adherent patients compared to the non-adherent patients. Table 3.3 in Appendix III describes the patient demographic and clinical characteristics in detail among adherent and non-adherent NOAC patients.

Comparison of Annual and Monthly All-cause AF related Healthcare (Drug cost, Inpatient, Outpatient and total) Costs [NOAC vs. Warfarin cohort]

The annual AF related all-cause healthcare costs (inpatient, medical, total) were calculated based on the GLM model using the gamma distribution since we expected a skewed distribution of the cost and the gamma model being acceptable approach handling the cost data.[18]

As expected, the annual drug cost for warfarin users was significantly lower compared to the NOAC users (331 vs. 4988) since the NOACs are branded drugs and warfarin is generic on the market. However, the medical cost which included all inpatient and outpatient costs were significantly higher ($31,400 vs. $22,134) for patients on warfarin therapy as compared to the NOAC users. The individual inpatient cost for warfarin users was $25,405 compared $15,362 for patients taking NOACs.

The total healthcare cost consists of the sum of all drug cost (including copays and deductibles), inpatient cost, outpatient cost (including the professional fees, and cost of INR monitoring specifically for the warfarin users). The total annual adjusted AF-related cost for warfarin users was significantly higher than NOAC users ($32,157 vs. $26,803). Overall, the high drug cost for NOAC users was offset by higher inpatient and outpatient costs (medical costs) for warfarin users.

A similar trend was observed for the monthly all-cause total cost (+ $388) and medical costs (+ $773) significantly greater for warfarin users compared to the NOAC users. Please refer to Table 3.4 and 3.5 in Appendix III for detailed results.

Comparison of Healthcare Resource Utilization (NOAC vs. Warfarin cohort)

The adjusted estimates for annual ER visits for warfarin were similar compared to NOAC users (14 vs. 13, p=0.4607). Although, there was a significant difference in the number of annual office visits between warfarin and NOAC (76 vs. 49) users. Similar results with a higher ER (1.14 vs. 1.04) and office visits (6.37 vs. 4.11) was observed for the monthly estimates for warfarin vs. NOAC users. Please refer to Table 3.4 and 3.5 in Appendix III for detailed results.

Subgroup Analysis

The different components of the all-cause annual cost (including the drug, inpatients, medical costs) and HCRU were described across the subgroups. Age, gender, region, insurance type, CHA_2D_2VASC, and CCI were the major subgroups.

Comparison of Costs by Subgroups

Drug Cost

The drug cost was highest in the Northeast region for both warfarin and NOACs. Annual drug costs for the older patients was slightly higher compared to younger patients on NOACs (5284 vs. 5064). Patients with an independent coverage for NOACs and POS for warfarin had highest drug costs compared to other types of insurance (including HMO, PPO, EPO, and Others). As expected, the drug cost for NOACs increased with the stroke risk. The patients on NOACs with moderate to high-risk CHA_2D_2VASC had higher drug cost compared to low-risk patients (5205 vs. 4941). A similar trend of increase in drug

cost based on higher CCI was observed for the NOAC users. Please refer to Table 3.6 in Appendix III for the detailed results.

Medical Cost (Inpatient and Outpatient costs)

Annual overall medical costs for NOAC or warfarin users was higher in males, patients with EPO insurance, 3+ comorbidities based on CCI and patients from the South. The numbers might be due higher proportion of males and patients from the South in the entire population. The medical cost for NOAC patients increased with severity by CCI ($19820 for CCI=0, $26396 for CCI=1-2, and $41144 for CCI $\geq$3).

On the contrary, the patients in the low-risk CHA_2D_2VASC group had slightly higher medical cost compared to the patients in the higher risk groups (36024 vs. 29247). Please refer to Table 3.7 in Appendix III for the detailed results.

Healthcare Resource Utilization

Annual ER visits for patients using warfarin were highest in the Midwest (16.6. For patients on the NOAC therapy, highest ER visits were in patients from the Northeast (18). The mean annual ER visits were higher in patients with age < 65 years' in both NOAC (13 vs. 7) and warfarin (16 vs. 10) user cohort. In both cohorts (warfarin and NOAC), ER visits were higher for patients with HMO and POS insurance. Mean annual ER visits were not significantly different across clinical severity based subgroups (CHA_2D_2VASC and CCI). Please refer to Table 3.8 in Appendix III for the detailed results.

Mean annual office visits were higher in females in both NOAC (52 vs. 46) and warfarin (79 vs. 74) user cohorts. Similarly, the office visits were higher among patients with

moderate to high stroke risk and for more severe patients with 3+ co-morbidities based on CCI in both NOAC and warfarin users. For NOAC patients, the office visit for mild vs. moderate-severe CHA_2D_2VASC score was 37 vs. 50 respectively. The NOAC users with Independent (Annual office visits 55) and PPO (Annual Office visits - 56) insurance had a higher number of office visits compared to other insurance types. Please refer to Table 3.9 and 3.10 in Appendix III for detail on HCRU by subgroups.

Overall Results

Highest cost drivers for drug cost for warfarin users was patients from Northeast. Conversely, highest cost drivers for medical cost were patients less than <65 years and patients with CCI +3.

For NOACs, the highest cost driver for the drugs was user who were 65 and above, from Northeast, $CHA_2DS_2VAS_C$ >2 (mod-high risk), and independent insurance. Additionally, medical cost was driven by EPO insurance and CCI+3.

Although ER visits (13.78 vs. 14.47), and inpatient costs ($20,756 vs. $23,208) were lower among the adherent patients, there was no significant difference in estimates between adherence and non-adherent patients.

Bleeding Related Costs

A total of 558 and 224 patients had bleeding related costs. Annual bleeding related drug cost was significantly higher for NOACs compared to warfarin ($6057 vs $3737). This trend was also consistent for monthly drug costs for NOACs vs Warfarin ($505 vs $311). Please refer to Table 3.14 in Appendix III for detail on HCRU by subgroups.

Similar to all cause AF related costs, the bleeding related medical cost for NOACs was lower ($1741 vs $6021) compared to warfarin.

The main cost drivers for bleeding related medical costs for warfarin were patients with Age <65 and patients with EPO insurance while the main drivers for NOACs users were higher CCI and EPO insurance. Please refer to Table 3.12 and 3.13 in Appendix III for detail on HCRU by subgroups.

Comparison of Annual HCRU and Costs by Adherence

As an exploratory analysis to generate a possible hypothesis, cost and HCRU were compared across adherent and non-adherent cohorts for NOAC users. The HCRU was compared between the adherent and non-adherent NOAC patients based on the 12-months of drug use. Although ER visits (10.59 vs. 12.68), inpatient costs ($24760 vs. $30549) and all-cause total cost ($34854 vs. $37821) was lower among the adherent patients, there was no significant difference between the estimates for adherence and non-adherent patients. Conversely, adherent patients had non-significantly higher office visits compared to the non-adherent patients. Please refer to Table 3.11 in Appendix III.

DISCUSSION

Our study found the economic burden of atrial fibrillation on anticoagulant users based on total annual healthcare cost was substantial (>$25,000). Moreover, the total annual healthcare costs for warfarin users was higher compared to the patients taking NOACs. The inpatient and outpatient costs for NOAC users were significantly lower compared to patients with warfarin therapy, which offset the higher drug costs for NOACs. Moreover, warfarin patients had higher ER and office visits (HCRU) compared to NOAC patients. Approximately, at least 60% of the total cost was attributed to the inpatient setting.

Our study was the first to investigate each of the cost (Medical, inpatient) and HCRU (ER and office visits) components among NOAC vs. warfarin users across clinically important subgroups. The results provided valuable insights to identify specific patient groups with high cost and HCRU and can help to plan targeted approaches and interventions. Also, the real world cost estimates can be used as cost input in further budget impact and cost-effectiveness studies.

Our study was also the first to explore an impact of medication adherence on cost and HCRU in AF patients. Although our study did not find any association of adherence with a decrease in cost, it indicates that increase in adherence does not lead to any additional use of economic resources. Further in-depth analysis using matched cohorts is warranted.

Our estimates of the healthcare costs (drug, medical, total) were consistent with the existing literature. Based on United States Department of Defense (DOD) Military Health System data, drug costs were higher ($4369, $p < 0.001$) for dabigatran compared to warfarin which is similar to our estimated drug costs.[19] Mercaldi et.al. compared an annual healthcare cost between patients without a major event ($15,718 in 2006 US

dollars) vs. patients who had an ischemic stroke, hemorrhagic stroke, or major bleeding ($43,937; $60,123; and $39,943 respectively).[20] Based on the MarketScan data (2003-2007), unadjusted all-cause health care costs in the 12 months after the warfarin index claim were $41,903 ($56,654), $40,586 ($65,164), and $24,347 ($56,488) for patients with at least 1 ICH, major GI bleeding, and minor GI bleeding, respectively, compared with $24,129 ($36,425) for subjects with no bleeding episodes.[21] Based on a combined data using two large administrative databases (Optum and Medicare), the total AF-related healthcare cost for patients aged 18 to 64 years was $38,861 (95% CI $35,781-$41,950).[22] Furthermore, a comprehensive review of the literature (PubMed and Medline search) resulted in total healthcare cost for AF from $18,454 to $38,270.[14] Although, it should be acknowledged that cost estimates reported in our analyses are adjusted using a multivariate model. In another study based on the Medicare beneficiaries, the healthcare costs for patients with ischemic stroke were $63,781 per patient and $64,596 for patients with hemorrhage versus $35,474 for patients without these events.[23] Higher drug cost for the NOACs can be explained by the fact that dabigatran and rivaroxaban are branded medications with higher co-pays. Lower inpatients and outpatient cost for NOACs can be attributed to a lower propensity of risk outcomes (strokes, recurrent DVTPE, bleeding, PE, etc.) in patients taking NOACs.

A study based on the claims data 2010-2011 reported, patients on dabigatran had fewer per-month ER visits (0.10 vs. 0.13, $P = 0.010$), and office visits (1.98 vs. 2.96, $P < 0.001$) compared to the patients on warfarin therapy.[24] Furthermore, in a study based on the Medicare data, the total outpatient visits for a 12-month period were 53.[25]

Our study found higher estimates which might be attributed to the inclusion of a higher proportion of patients with moderate to high-risk of stroke and CCI index of +3. Higher ER and office visits in warfarin might be due to the suboptimal utilization of INR testing lead to complications in regards to inadequate anticoagulation.

A study on warfarin users found no significant differences in costs and HCRU between adherent and non-adherent patients.[26] Based on our results, the above inference relates to the entire class of anticoagulants including the NOACs.

Our study was the first to compare the HCRU and cost between the NOAC and warfarin taking patients and to quantify the estimates across the demographic and clinical subgroups. The Northeast region had highest drug costs, which could be due to better healthcare and insurance availability (coverage) in the region. Annual overall medical costs for NOAC or warfarin patients was higher for patients with 3+ comorbidities based on CCI, and for patients from the South. Our study found higher cost was associated with lower age (<65) which is consistent with previous cost studies in AF.[22,27] It is important to note that younger patients might be aggressively treated than older patients for AF.

Our study identified higher burden of cost and resource utilization is incurred on specific subgroup of the patients taking NOACs e.g. total cost and ER visits were higher in males. The drug cost, inpatient costs, and HCRU were highest for patients in the Northeast region. The medical cost and HCRU were highest for the patients with POS insurance. Higher stroke risk and CCI score in NOAC users translated into higher costs and HCRU. These results provide valuable insight on the utilization of healthcare resources in regards to targeting specific population groups.

One of the advantages of the study was the use of large commercial database represented by population across the United States. All the cost reported were adjusted to 2016 according to the latest consumer price index (CPI) data released by US government. It should be considered that even though generic warfarin is cheaper than warfarin, the cost of regular INR monitoring is an additional cost for the warfarin users. Our study found a total of 2464 patients (74%) who checked their INR and had an average cost of $120 per person per year. We also included INR monitoring costs for calculating the total healthcare costs. The healthcare costs, including the inpatient, medical, and total cost were adjusted using the gamma model; the crude confidence intervals were obtained by exponentiating the estimates.

The aim of the subgroup analysis and comparison of adherence based cohorts was targeted at hypothesis generation, and thus, any disease specific (GI related, stroke related) costs were not examined. All-cause costs were estimated to understand the landscape and economic burden in the AF-related population. The estimates for drug cost, HCRU, and medical costs can be applied to the economic models, while the estimates based on the comparison between adherent and non-adherent samples can be helpful for meta-analyses and indirect comparisons. Further studies can be planned in regards to event-specific estimates (related to stroke, bleeding, DVTPE) and cost-effectiveness analysis.

It should be noted that the costs estimated in our subgroup analysis were not adjusted. Although cost estimates (inpatient, medical, total cost) were adjusted using GLM models, there was no matching performed on NOAC vs. warfarin cohort, so there might be a possibility of selection bias due to unmeasured factors in regards to the sample

populations. Use of a large administrative database may not be generalizable as it is mostly represented by commercially insured population. Furthermore, use of claims data may lead to reliance on diagnosis, coding and lack of clinical details. In our cohort with 12 months of follow-up assessment, most of the drug prescriptions were accounted for the years 2010-2011 (2010 – Warfarin – 1438, NOAC-178 and 2011 warfarin – 1829, NOAC=1583), with very few patients in 2012 due to criteria for a follow-up of 12 months. Hence, further analysis with longer follow-up time may help to capture details and specific patterns.

Accepting these limitations, our results can be used to help support reimbursement decisions and help generate hypothesis for more comprehensive studies. Inputs can be helpful in the further economic analysis and meta-analyses.

CONCLUSION

The study helps to estimate the substantial economic burden of AF in warfarin and NOAC users. The higher drug cost of NOACs was offset by the lower inpatient and outpatient costs and HCRU for the NOAC users as compared to warfarin users. There is no significant difference in costs and HCRU (except office visits) between adherent and non-adherent NOAC patients. The study provides valuable insight, identifying specific subgroups (e.g. Patients from the Northeast/South, less than 65, HMO/POS and a higher severity based on CHA_2D_2VASC and CCI) with a higher burden of cost and resource utilization in warfarin and NOAC users. These results could help the decision makers to balance the risk over benefit, and consider the cost associated with an optimal therapeutic choice of anticoagulants. Further research on the use of NOACs in regards to the specific outcomes and its cost-effectiveness is warranted.

Figure 3.1 Study Cohort

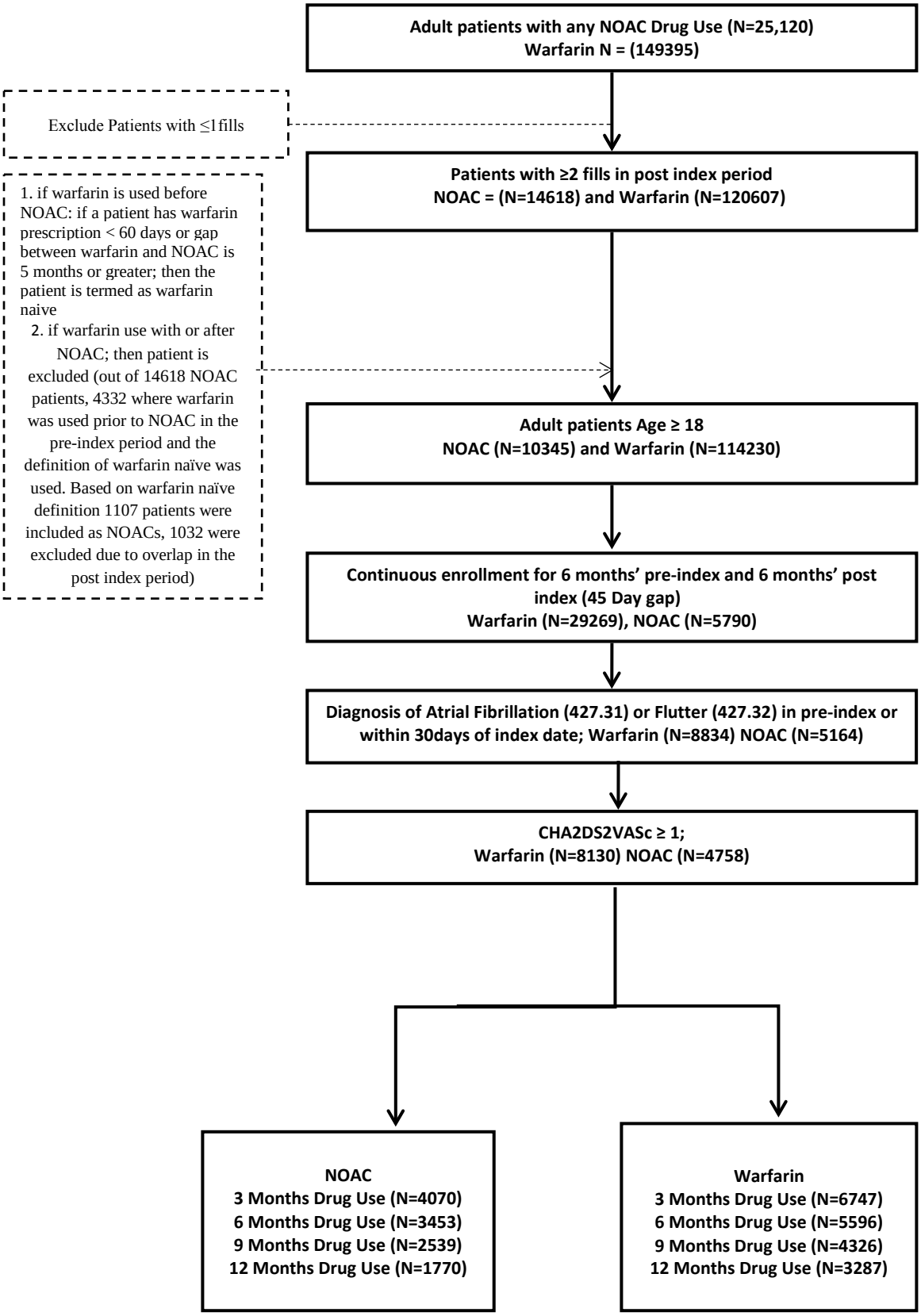


Table 3.1 Patient Demographic and Clinical Characteristic of NOAC vs Warfarin patients at 12-month assessment period

Variable Description	Statistic Response Category	Total (N= 5,057)	NOACs (N= 1,770)	Warfarin (N= 3,287)	P-value (Chi-sq)
Age at index date	N	5057	1,770	3,287	<0.001
	Mean (SD)	65.94 (11.61)	65.2 (10.56)	66.34 (12.13)	
	Median(IQR)	64 (58-75)	64 (59,73)	65 (58,76)	
	Range	18-86	26,86	18,86	
Gender	Female	1,718 (33.97)	544 (30.73)	1,174 (35.72)	0.0004
	Male	3,339 (66.03)	1,226 (69.27)	2,113 (64.28)	
Insurance type	EPO	512 (10.12)	204 (11.53)	308 (9.37)	
	HMO	312 (6.17)	103 (5.82)	209 (6.36)	
	IND	1,030 (20.37)	280 (15.82)	750 (22.82)	
	Others	7 (0.14)	0 (0.00)	7 (0.21)	
	POS	2,945 (58.24)	1,104 (62.37)	1,841 (56.01)	
	PPO	251 (4.96)	79 (4.46)	172 (5.23)	
Region	Midwest	1,469 (29.05)	388 (21.92)	1,081 (32.89)	<0.001
	Northeast	534 (10.56)	168 (9.49)	366 (11.13)	
	South	2,134 (42.20)	908 (51.30)	1,226 (37.30)	
	West	920 (18.19)	306 (17.29)	614 (18.68)	
Stroke risk (CHA2D2VASC)	low risk	1,762 (34.84)	697 (39.38)	1,065 (32.40)	<0.001
	mod-high risk	3,295 (65.16)	1,073 (60.62)	2,222 (67.60)	
CCI category	CCI score 0	715 (14.14)	311 (17.57)	404 (12.29)	<0.001.
	CCI score 1-2	2,140 (42.32)	851 (48.08)	1,289 (39.22)	
	CCI score 3 and+	2,202 (43.54)	608 (34.35)	1,594 (48.49)	
Statin use	Yes	2478(49.0)	917(51.81)	1561 (47.49)	0.003
	No	2579 (51.0)	853 (48.19)	1726 (52.51)	
ACE ARB Inhibitor	Yes	2382 (47.10)	874 (49.38)	1508 (45.88)	0.017
	No	2675 (52.90)	896 (50.62)	1779 (54.12)	
Beta-blocker	Yes	1392 (27.53)	536(30.28)	856 (26.04)	0.001
	No	3665 (72.47)	1234 (69.72)	2431(73.93)	

CCI- Charlson's comorbidity Index, HMO – Health maintenance organization, PPO- Preferred provider organization, EPO - Exclusive provider organizations, IND- Independent, POS-Point of service, ARB- Angiotensin Receptor Blocker, ACE- Angiotensin-converting enzyme

Table 3.2 Adherence Measured by PDC at Different Time-points

Adherence	N	Adherence NOACs	N	Adherence Warfarin	p-value
6 months	3453	2859 (82.80%)	5596	4063 (72.61%)	<0.001
12 months	1770	1388 (78.42%)	3287	2034 (61.88%)	<0.001

*PDC ≥ 80 = Adherent, Adherence measured by PDC at different time points

Table 3.3 Patient Demographic and Clinical Characteristics of Adherent Vs Non-adherent NOAC patients at 12-month Assessment Period

Variable Description	Statistic Response Category	Total (N= 1,770)	Adherent (N= 1,388)	Non-Adherent (N= 382)	p-value
Age at index date	N	1770	1,388	382	<.0001
	Mean (SD)	65.20 (10.55)	66.02 (10.16)	62.24 (11.42)	
	Median(IQR)	64 (59, 73)	64 (59,73)	62 (55,68)	
	Range	26,83	34,86	26,86	
Gender	Female	544 (30.73)	426 (30.69)	118 (30.89)	0.9407
	Male	1,226 (69.27)	962 (69.31)	264 (69.11)	
Insurance type	EPO	204 (11.53)	143 (10.30)	61 (15.97)	<0.001
	HMO	103 (5.82)	73 (5.26)	30 (7.85)	
	IND	280 (15.82)	239 (17.22)	41 (10.73)	
	POS	1,104 (62.37)	862 (62.10)	242 (63.35)	
	PPO	79 (4.46)	71 (5.12)	8 (2.09)	
Region	Midwest	388 (21.92)	317 (22.84)	71 (18.59)	0.0487
	Northeast	168 (9.49)	132 (9.51)	36 (9.42)	
	South	908 (51.30)	689 (49.64)	219 (57.33)	
	West	306 (17.29)	250 (18.01)	56 (14.66)	
Stroke risk (CHA2D2VASC)	Low risk	697 (39.38)	515 (37.10)	182 (47.64)	0.0002
	Mod-high risk	1073 (60.62)	873 (62.90)	200 (54.36)	
CCI Category	CCI score 0	311 (17.57)	239 (17.22)	72 (18.84)	0.5734
	CCI score 1-2	851 (48.08)	676 (48.70)	175 (45.81)	
	CCI score 3 and+	608 (34.35)	473 (34.08)	135 (35.34)	
Statin Use	No	853 (48.19)	636 (45.82)	217 (56.81)	0.0001
	Yes	917 (51.81)	752 (54.18)	165 (43.19)	
ACE ARB Inhibitor Use	No	896 (50.62)	688 (49.57)	208 (54.45)	0.0910
	Yes	874 (49.38)	700 (50.43)	174 (45.55)	
Beta-blocker Use	No	1,234 (69.72)	980 (70.61)	254 (66.49)	0.1213
	Yes	536 (30.28)	408 (29.39)	128 (33.51)	

Variable Description	Statistic Response Category	Total (N= 1,770)	Adherent (N= 1,388)	Non-Adherent (N= 382)	p-value

CCI- Charlson's comorbidity Index, HMO – Health maintenance organization, PPO- Preferred provider organization, EPO - Exclusive provider organizations, IND- Independent, POS-Point of service, ARB- Angiotensin Receptor Blocker, ACE- Angiotensin-converting enzyme

Table 3.4: Annual Cost by Type and Drug Class

Drug	Cost Type	Average Cost*	Upper 95%CI	Lower 95%CI	p-value
Warfarin	Drug Cost	$331	$361	$303	<.0001
NOAC		$4,988	$5,464	$4,554	
Warfarin	Medical Cost	$31,400	$36,548	$26,977	<.0001
NOAC		$22,134	$25,876	$18,933	
Warfarin	Inpatient Cost	$25,405	$31,197	$20,688	<.0001
NOAC		$15,362	$19,060	$12,381	
Warfarin	Total Cost	$32,157	$37,029	$27,925	<.0001
NOAC		$26,803	$30,989	$23,182	
Warfarin	ER Visits	14	18	11	0.4286
NOAC		13	17	9	
Warfarin	Office Visits	76	85	69	<.0001
NOAC		49	55	44	

*The costs presented in the above tables are adjusted using GLM model using gamma distribution. The total cost of INR monitoring among warfarin users is $120 per year (n=2464) is calculated separately and is included in the total cost.

Table 3.5: Monthly Cost by Type and Drug Class

Drug	Cost Type	Average Cost*	Upper 95%CI	Lower 95%CI	p-value
Warfarin	Drug Cost	$28	$30	$25	<.0001
NOAC		$416	$455	$379	
Warfarin	Medical Cost	$2,617	$3,046	$2,248	<.0001
NOAC		$1,844	$2,156	$1,578	
Warfarin	Inpatient Cost	$2,117	$2,600	$1,724	<.0001
NOAC		$1,280	$1,588	$1,032	
Warfarin	Total Cost	$2,680	$3,086	$2,327	<.0001
NOAC		$2,234	$2,582	$1,932	
Warfarin	ER Visits	1.14	1.49	0.87	0.4286
NOAC		1.04	1.43	0.76	
Warfarin	Office Visits	6.37	7.07	5.74	<.0001
NOAC		4.11	4.58	3.69	

*The costs presented in the above tables are adjusted using GLM model using gamma distribution. The total cost of INR monitoring among warfarin users is $10 per month (n=2464) is calculated separately and is included in the total cost

Table 3.6 Annual Drug Cost by Subgroup and Drug Class

Subgroup	Drug Class	Category	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
Gender	Warfarin	Female	1174	1168	354.04	312.83	278.46	4.11	3148.81
		Male	2113	2104	340.91	281.59	283.69	9.11	3552.00
	NOAC	Female	544	543	5078.49	1847.40	5179.27	273.70	10555.10
		Male	1226	1221	5201.73	1847.40	5323.20	273.70	12028.14
Region	Warfarin	Northeast	366	361	388.02	328.98	311.98	16.45	2277.69
		Midwest	1081	1081	337.66	280.87	282.13	4.11	3552.00
		South	1226	1220	355.60	308.29	284.82	9.11	2938.84
		West	614	610	314.57	255.14	259.20	9.88	2909.16
	NOAC	Northeast	168	168	5277.96	1905.65	5489.09	273.70	9032.22
		Midwest	388	387	5160.54	1796.92	5259.27	273.70	12028.14
		South	908	904	5117.97	1817.63	5198.69	273.70	9786.22
		West	306	305	5240.89	1967.81	5384.12	274.54	10555.10
Age	Warfarin	Less than 65	1621	1619	363.76	317.27	296.19	9.11	3552.00
		65 and above	1666	1653	327.81	266.31	266.08	4.11	2909.16
	NOAC	Less than 65	967	966	5064.21	1856.19	5155.56	273.70	10179.17
		65 and above	803	798	5284.35	1831.41	5467.06	273.70	12028.14
Insurance	Warfarin	EPO	308	307	352.87	277.36	289.91	14.69	2219.53
		HMO	209	209	348.77	288.05	291.47	10.42	2192.64
		IND	750	743	311.74	265.97	242.79	12.48	2909.16
		OTH	7	7	285.46	116.89	338.27	52.77	401.94
		POS	1841	1840	359.33	305.98	290.92	4.11	3552.00
		PPO	172	166	330.07	293.99	294.81	9.88	2800.44
	NOAC	EPO	204	204	5012.03	1999.75	5162.89	313.70	9073.53
		HMO	103	103	4913.11	2015.80	5030.56	333.70	9231.90
		IND	280	278	5446.05	1901.29	5564.18	273.70	12028.14
		POS	1104	1103	5142.91	1772.55	5179.27	273.70	10179.17
		PPO	79	76	5181.57	1984.58	5455.72	273.70	9032.22
	Warfarin	Low risk	436	435	388.35	365.95	299.07	12.22	2800.44

Chads2		Mod-high risk	2851	2837	339.04	279.81	278.26	4.11	3552.00
	NOAC	Low risk	278	278	4941.17	1863.25	5060.59	313.70	9576.13
		Mod-high risk	1492	1486	5205.45	1842.48	5339.76	273.70	12028.14
CCI	Warfarin	CCI score 0	404	404	361.20	377.90	270.87	14.79	3552.00
		CCI score 1-2	1289	1284	338.73	270.59	287.06	9.11	2800.44
		CCI score 3 and+	1594	1584	347.19	285.95	280.75	4.11	2938.84
	NOAC	CCI score 0	311	310	5014.82	1962.94	5186.12	273.70	10179.17
		CCI score 1-2	851	848	5200.81	1827.30	5267.87	273.70	10555.10
		CCI score 3 and+	608	606	5188.22	1814.55	5339.27	274.54	12028.14

Table 3.7 Annual Medical Cost (Inpatient + Outpatient) by Subgroup and Drug Class

Subgroup	Drug Class	Gender	N Obs	N	Mean	Std Dev	Median	Min	Maximum
Gender	Warfarin	Female	1174	1174	47168.99	89846.58	21340.52	215.93	1147512.98
		Male	2111	2111	55250.38	126739.3	21003.33	20.91	2081065.33
	NOAC	Female	544	544	29140.59	38510.35	15955.13	160.94	392835.74
		Male	1225	1225	30833.15	61775.08	14701.66	232.99	1652255.80
Region	Warfarin	Northeast	366	366	43149.24	67505.72	21221.89	1038.5	810134.03
		Midwest	1080	1080	45867.41	94433.27	20044.85	336.36	1271323.63
		South	1225	1225	58866.35	128163.8	23370.72	20.91	2081065.33
		West	614	614	56301.71	139224.1	20185.02	96.72	1842247.09
	NOAC	Northeast	168	168	29891.14	44790.03	16746.95	301.67	392835.74
		Midwest	387	387	28238.03	36556.32	15792.93	231.00	347369.24
		South	908	908	31988.93	66846.50	15491.25	160.94	1652255.80
		West	306	306	28193.82	43153.67	13043.94	239.36	400422.86
Age	Warfarin	Less than 65	1620	1620	66859.90	148070.8	23318.95	20.91	2081065.33
		65 and above	1665	1665	38256.40	65973.35	20156.99	96.72	919247.71
	NOAC	Less than 65	967	967	34682.07	68665.02	16249.84	160.94	1652255.80
		65 and above	802	802	25044.30	33184.19	13816.1	231.00	434644.18
Region	Warfarin	EPO	308	308	63486.28	151724.61	24402.41	1581.57	1842247.09
		HMO	209	209	64412.09	127540.03	17072.87	791.48	998725.56
		IND	750	750	33043.61	56963.08	19703.58	309.05	1082104.45
		OTH	7	7	18523.34	19706.42	13936.98	2367.18	56630.46
		POS	1840	1840	58275.45	126602.58	22022.87	20.91	2081065.33
		PPO	171	171	40086.85	59660.44	20604.25	215.93	525007.47
	NOAC	EPO	204	204	41627.80	121491.17	14373.22	287.06	1652255.80
		HMO	103	103	27131.50	30526.27	13706.97	360.88	158301.04
		IND	280	280	22299.83	23890.75	14345.6	488.40	154088.76
		POS	1103	1103	31034.30	43772.63	15888.65	160.94	434644.18
		PPO	79	79	23565.72	29082.37	11068.98	1224.9	154167.08

Chads2	Warfarin	Low risk	435	435	47065.99	124622.72	17772.68	20.91	2081065.33
		Mod-high risk	2850	2850	53170.61	113430.16	21630.34	96.72	1842247.09
	NOAC	Low risk	278	278	36024.49	106001.65	14074.62	160.94	1652255.80
		Mod-high risk	1491	1491	29247.67	39748.58	15477.46	231.00	434644.18
CCI	Warfarin	CCI score 0	402	402	19878.22	30131.87	10061.59	96.72	274525.38
		CCI score 1-2	1289	1289	33107.30	74092.66	16511.74	20.91	2081065.33
		CCI score 3 and+	1594	1594	76125.22	146466.61	32284.13	215.93	1842247.09
	NOAC	CCI score 0	310	310	19819.83	27390.49	9696.85	160.94	179454.06
		CCI score 1-2	851	851	26396.24	37887.51	13151.84	231.00	434644.18
		CCI score 3 and+	608	608	41144.31	80226.92	22435.48	301.67	1652255.80

Table 3.8. Annual Inpatient Cost by Subgroup and Drug Classes

Subgroup	Drug Class	Subgroup	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
Gender	Warfarin	Female	569	569	39942.35	79794.05	15156.45	35.18	1010478.85
		Male	928	928	54957.10	135035.32	19506.5	28.06	1910471.44
	NOAC	Female	189	189	23653.22	29106.53	12239.85	12.78	204592.61
		Male	376	376	27334.06	38633.13	12741.74	50.08	381637.34
Region	Warfarin	Northeast	173	173	36692.14	65881.37	17069.78	106.15	753940.11
		Midwest	501	501	39085.00	76070.93	14812.88	35.18	715110.02
		South	552	552	62783.34	146125.13	22786.9	260.26	1910471.44
		West	271	271	48493.19	136272.44	14378.71	28.06	1807675.41
	NOAC	Northeast	56	56	27776.63	33892.66	10655.19	131.87	152263.47
		Midwest	135	135	25853.79	30525.88	13088.99	17.31	148662.21
		South	275	275	27012.33	38555.11	13399.44	50.08	381637.34
		West	99	99	22968.91	35565.55	10153.53	12.78	204592.61
Age	Warfarin	Less than 65	713	713	73664.40	155664.23	30334.14	198.68	1910471.44
		65 and above	784	784	27046.77	56902.01	11681.34	28.06	842068.51
	NOAC	Less than 65	303	303	32673.05	42153.26	17789.68	50.08	381637.34
		65 and above	262	262	18504.32	24435.41	9373.92	12.78	148662.21
Region	Warfarin	EPO	140	140	71822.23	184891.04	27120.22	871.24	1807675.41
		HMO	93	93	72514.07	119336.20	28831.58	1272.23	591538.44
		IND	372	372	18568.98	21972.65	11154.1	28.06	218371.22
		OTH	4	4	8497.43	7266.26	6720	2104.01	18445.72
		POS	811	811	58668.65	129980.99	21515.12	82.00	1910471.44
		PPO	77	77	31253.75	35900.20	15346.6	613.11	167665.10
	NOAC	EPO	62	62	41956.95	63342.91	24441.25	50.08	381637.34
		HMO	37	37	22890.85	24711.01	11579.86	410.14	113688.69
		IND	103	103	14577.70	17908.27	8922.69	17.31	106211.49
		POS	342	342	27570.64	33554.29	13502.13	12.78	204592.61
		PPO	21	21	17576.78	16408.66	12376.95	3510.34	67241.71
	Warfarin	Low risk	163	163	58787.54	168153.40	25051.38	387.14	1910471.44

Chads2		Mod-high risk	1334	1334	48084.72	109565.61	16130.49	28.06	1807675.41
	NOAC	Low risk	80	80	37532.69	53030.35	20178.46	503.08	381637.34
		Mod-high risk	485	485	24217.42	31698.79	11596.29	12.78	287687.38
CCI	Warfarin	CCI score 0	81	81	22724.00	28764.43	13705.23	383.73	218371.22
		CCI score 1-2	440	440	36583.27	102815.09	15000.34	35.18	1910471.44
		CCI score 3 and+	976	976	57161.99	126911.72	19216.51	28.06	1807675.41
	NOAC	CCI score 0	60	60	20290.43	17632.32	12035.4	1549.40	69858.01
		CCI score 1-2	232	232	23408.02	30214.18	11685.66	12.78	204592.61
		CCI score 3 and+	273	273	29670.25	42194.49	14008.55	17.31	381637.34

Table 3.9 . Annual ER Count by Subgroup and Drug Class

Subgroup	Drug Class	Subgroup	N Obs	N	Mean	Std Dev	Median	Min	Maximum
Gender	Warfarin	Female	1174	143	14.87	21.61	5	1	109
		Male	2111	269	13.13	25.41	4	1	318
	NOAC	Female	544	68	10.63	16.95	4	1	92
		Male	1225	143	11.24	16.98	3	1	82
Region	Warfarin	Northeast	366	41	8.73	15.18	3	1	84
		Midwest	1080	157	16.64	21.15	6	1	109
		South	1225	145	13.13	19.93	3	1	106
		West	614	69	11.36	38.47	3	1	318
	NOAC	Northeast	168	10	18.00	25.12	4.5	1	75
		Midwest	387	49	12.80	14.84	8	1	80
		South	908	114	8.29	12.34	2	1	59
		West	306	38	15.21	25.77	3	1	92
Age	Warfarin	Less than 65	1620	265	16.00	27.64	5	1	318
		65 and above	1665	147	9.65	15.28	3	1	84
	NOAC	Less than 65	967	133	13.50	19.03	5	1	92
		65 and above	802	78	6.85	11.52	3	1	75
Region	Warfarin	EPO	308	43	8.07	14.47	2	1	64
		HMO	209	70	19.33	20.73	12.5	1	90
		IND	750	38	8.79	20.39	3	1	109
		OTH	7	5	21.20	16.13	25	1	41
		POS	1840	239	13.90	27.06	4	1	318
		PPO	171	17	11.59	18.75	6	1	72
	NOAC	EPO	204	24	7.17	9.40	2.5	1	33
		HMO	103	21	10.67	17.79	4	1	80
		IND	280	21	6.43	7.53	2	1	21
		POS	1103	138	12.51	18.84	3	1	92
		PPO	79	7	10.43	12.83	7	1	37
Chads2	Warfarin	Low risk	435	71	14.58	18.10	5	1	87
		Mod-high risk	2850	341	13.56	25.24	4	1	318

	NOAC	Low risk	278	31	10.03	13.33	2	1	44
		Mod-high risk	1491	180	11.22	17.50	3	1	92
CCI	Warfarin	CCI score 0	402	56	13.84	19.51	3	1	87
		CCI score 1-2	1289	165	13.21	20.08	4	1	109
		CCI score 3 and+	1594	191	14.16	28.33	5	1	318
	NOAC	CCI score 0	310	39	12.26	19.41	3	1	92
		CCI score 1-2	851	101	10.64	16.02	3	1	75
		CCI score 3 and+	608	71	10.94	16.97	4	1	82

Table 3.10 Annual Office Visits by Subgroup and Drug Class

Subgroup	Drug Class	Subgroup	N Obs	N	Mean	Std Dev	Median	Min	Maximum
Gender	Warfarin	Female	1174	1173	79.43	61.78	66	1	875
		Male	2111	2108	73.79	62.55	60	1	860
	NOAC	Female	544	543	52.23	44.85	40	1	428
		Male	1225	1225	45.65	44.23	35	1	773
Region	Warfarin	Northeast	366	366	79.24	63.79	63	1	473
		Midwest	1080	1077	70.00	61.63	57	1	875
		South	1225	1224	82.46	64.73	68	2	723
		West	614	614	70.66	56.14	56.5	1	481
	NOAC	Northeast	168	168	51.47	45.61	39	1	337
		Midwest	387	387	41.97	33.17	32	3	274
		South	908	908	48.70	45.76	38	1	773
		West	306	305	49.76	51.71	36	3	428
Age	Warfarin	Less than 65	1620	1620	77.37	65.22	63	1	875
		65 and above	1665	1661	74.28	59.35	60	1	481
	NOAC	Less than 65	967	967	44.20	39.22	34	2	428
		65 and above	802	801	51.86	49.87	39	1	773
Region	Warfarin	EPO	308	308	83.08	62.83	70	3	423
		HMO	209	209	90.64	98.40	68	2	875
		IND	750	747	70.79	52.85	58	1	323
		OTH	7	7	97.29	74.67	128	1	199
		POS	1840	1839	74.83	60.00	61	1	723
		PPO	171	171	76.16	63.93	63	1	473
	NOAC	EPO	204	204	47.34	37.61	38	3	254
		HMO	103	103	46.87	30.50	41	8	170
		IND	280	279	55.28	48.16	41	1	296
		POS	1103	1103	45.27	44.42	34	2	773
		PPO	79	79	56.16	59.06	38	1	390
Chads2	Warfarin	Low risk	435	435	67.77	50.43	53	2	282
		Mod-high risk	2850	2846	77.03	63.87	62	1	875
	NOAC	Low risk	278	278	37.38	34.10	27	2	263

		Mod-high risk	1491	1490	49.59	45.95	38	1	773
CCI	Warfarin	CCI score 0	402	400	63.74	48.39	51	1	391
		CCI score 1-2	1289	1287	69.15	55.83	56	1	875
		CCI score 3 and+	1594	1594	84.21	68.93	67	1	860
	NOAC	CCI score 0	310	310	37.38	42.22	26.5	1	428
		CCI score 1-2	851	850	44.32	44.71	32	2	773
		CCI score 3 and+	608	608	57.60	43.55	46	1	337

Table 3.11: Comparison of Annual HCRU by Adherence

NOAC (Mean)	Adherence (n=1388)	Non Adherence (n=382)	T-test p-value
Annual ER	10.59 (16.32)	12.68 (9.11)	0.5047
Annual Office Visit	49.07 (46.89)	42.56 (34.10)	0.0026
Annual Inpatient Cost	24760.67 (34102.33)	30549.13 (40547.51)	0.1038
Annual All Cost	34854.65 (57328.97)	37821.67 (49239.30)	0.3156
NOAC (Median)	Adherence (n=1388)	Non Adherence (n=382)	p-value for median
Annual ER	3	4	0.6069
Annual Office Visit	37	34	0.1716
Annual Inpatient Cost	15962.44	11635.74	0.0554
Annual All Cost	18844.03	20853.42	0.4257

*The above estimated are unadjusted

Table 3.12 Annual Bleeding related Drug Cost by Subgroup and Drug Class

Subgroup	Drug Class	Category	N Obs	N	Mean	Std Dev	Median	Min	Maximum
Gender	Warfarin	Female	192	192	2740.61	7905.73	364.38	48.68	49118.13
		Male	366	366	4259.49	23696.38	392.19	27.06	403365.50
	NOAC	Female	72	72	5930.70	1995.49	5763.31	1737.75	14101.54
		Male	152	152	6116.05	3235.18	5784.74	923.43	28342.81
Region	Warfarin	Northeast	65	65	4188.57	11918.79	406.60	59.41	75025.93
		Midwest	159	159	2315.98	7756.81	342.54	42.59	62057.99
		South	227	227	4714.82	29005.37	410.59	27.06	403365.50
		West	107	107	3499.15	8627.67	390.95	54.56	41743.37
	NOAC	Northeast	16	16	6481.00	1858.66	6792.69	2509.63	8985.12
		Midwest	54	54	5602.66	1960.57	5416.12	2667.63	14101.54
		South	103	103	6273.41	3683.59	5814.43	923.43	28342.81
		West	51	51	5965.67	2029.72	5791.47	1737.75	13924.84
Age	Warfarin	Less than 65	242	242	5697.99	28893.37	416.62	53.90	403365.50
		65 and above	316	316	2234.99	6748.45	360.69	27.06	75025.93
	NOAC	Less than 65	97	97	5856.11	2925.96	5646.68	942.61	23974.32
		65 and above	127	127	6209.50	2867.54	5840.47	923.43	28342.81
Insurance	Warfarin	EPO	59	59	5043.53	10451.37	399.67	80.77	43167.92
		HMO	35	35	1622.85	4663.52	501.27	27.06	27456.84
		IND	137	137	1985.54	4927.44	357.37	42.59	38018.60
		OTH	1	1	236.03	.	236.03	236.03	236.03
		POS	301	301	4383.01	25836.95	377.11	35.83	403365.50
		PPO	25	25	5570.52	15332.13	370.50	47.00	75025.93
	NOAC	EPO	22	22	7430.97	6452.79	5712.34	942.61	28342.81
		HMO	9	9	5332.71	1595.41	5339.27	2667.12	7348.76
		IND	60	60	6284.54	2169.82	6033.79	923.43	15482.49
		POS	121	121	5836.43	2201.33	5805.15	1065.84	19296.20
		PPO	12	12	5157.80	2040.97	5075.56	2733.34	8985.12
Chads2	Warfarin	Low risk	49	49	2899.28	8084.75	419.81	53.90	49118.13
		Mod-high risk	509	509	3817.50	20524.96	380.41	27.06	403365.50
	NOAC	Low risk	19	19	5172.08	1856.43	5357.74	1737.75	8944.33

		Mod-high risk	205	205	6138.44	2959.32	5799.27	923.43	28342.81
CCI	Warfarin	CCI score 0	38	38	734.08	1465.53	310.32	47.00	8258.32
		CCI score 1-2	148	148	3212.20	7586.26	416.62	48.68	43167.92
		CCI score 3 and+	372	372	4252.34	23687.12	380.50	27.06	403365.50
	NOAC	CCI score 0	21	21	5568.80	1829.57	5805.15	1737.75	8944.33
		CCI score 1-2	81	81	5751.04	1392.35	5840.51	1065.84	9047.41
		CCI score 3 and+	122	122	6343.21	3659.25	5684.40	923.43	28342.81

Table 3.13 Annual Bleeding related Medical Cost by Subgroup and Drug Classes

Subgroup	Drug Class	Subgroup	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
Gender	Warfarin	Female	192	192	5189.20	12711.48	1259.24	4.07	125233.25
		Male	366	366	6457.84	25461.51	1077.17	12.71	408067.70
	NOAC	Female	72	72	1295.20	2121.46	614.51	11.07	11774.24
		Male	152	152	1951.46	4109.36	524.12	6.97	30620.42
Region	Warfarin	Northeast	65	65	6320.01	14652.69	960.81	13.36	75747.39
		Midwest	159	159	5420.93	14969.78	1191.54	15.69	154998.39
		South	227	227	7119.20	30478.76	1292.56	4.07	408067.70
		West	107	107	4402.89	8677.46	747.26	12.78	42233.69
	NOAC	Northeast	16	16	1212.51	1308.91	609.38	117.35	4510.60
		Midwest	54	54	1241.79	1823.59	566.67	32.54	9181.67
		South	103	103	2302.05	4865.62	482.44	11.04	30620.42
		West	51	51	1300.15	2066.49	632.05	6.97	11008.88
Age	Warfarin	Less than 65	242	242	8948.33	31750.58	1262.04	4.07	408067.70
		65 and above	316	316	3779.75	8179.94	1061.46	12.71	75747.39
	NOAC	Less than 65	97	97	1832.36	3696.29	666.25	11.07	27285.57
		65 and above	127	127	1670.37	3538.28	495.53	6.97	30620.42
Region	Warfarin	EPO	59	59	8661.58	18820.37	1379.70	4.07	125233.25
		HMO	35	35	4437.42	6620.89	902.49	4.65	27540.98
		IND	137	137	3043.52	5578.41	917.93	13.36	38361.65
		OTH	1	1	98.18	.	98.18	98.18	98.18
		POS	301	301	7021.24	27906.40	1168.57	11.04	408067.70
		PPO	25	25	6524.02	15461.24	1297.58	15.69	75747.39
	NOAC	EPO	22	22	4605.22	8405.55	789.95	47.64	30620.42
		HMO	9	9	538.57	890.17	163.39	50.54	2812.62
		IND	60	60	1305.04	2288.43	302.06	16.85	11598.13
		POS	121	121	1579.76	2678.94	625.12	6.97	18073.07
		PPO	12	12	1188.38	1298.64	784.22	36.60	4510.60
Chads2	Warfarin	Low risk	49	49	4103.06	8378.18	941.24	30.21	50078.34
		Mod-high risk	509	509	6205.98	22801.92	1157.85	4.07	408067.70
	NOAC	Low risk	19	19	1104.88	1808.94	541.42	16.85	8129.39
		Mod-high risk	205	205	1799.43	3720.12	565.24	6.97	30620.42

CCI	Warfarin	CCI score 0	38	38	2391.12	4049.39	767.54	15.69	18659.21
		CCI score 1-2	148	148	4736.61	9055.30	1075.58	4.07	55204.71
		CCI score 3 and+	372	372	6903.26	26165.31	1286.70	4.65	408067.70
	NOAC	CCI score 0	21	21	1827.97	2848.54	558.27	6.97	10951.24
		CCI score 1-2	81	81	1109.29	1856.28	384.86	32.53	11783.91
		CCI score 3 and+	122	122	2144.56	4453.81	695.94	11.07	30620.42

Table 3.14: Comparison of Annual and Monthly Bleeding related costs

	Drug Cohort	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
Annual Drug Cost	Warfarin	558	558	3736.86	19746.25	381.23	27.06	403365.50
	NOAC	224	224	6056.47	2891.79	5784.74	923.43	28342.81
Monthly Drug Cost	Warfarin	558	558	311.41	1645.52	31.77	2.25	33613.79
	NOAC	224	224	504.71	240.98	482.06	76.95	2361.90
Monthly medical	Warfarin	558	558	501.78	1826.87	93.66	0.34	34005.64
	NOAC	224	224	145.04	300.02	47.04	0.58	2551.70
Annual Medical cost	Warfarin	558	558	6021.32	21922.43	1123.86	4.07	408067.70
	NOAC	224	224	1740.52	3600.26	564.52	6.97	30620.42

APPENDICES III

Appendix 3 Table 1: ICD-9 Diagnosis Codes

		ICD-9 Codes
AF Diagnosis	*Atrial Fibrillation and Flutter*	*427.31, 427.32*
	Hypothyroidism	*240.9*
CHA2DS2VASC Score	*Congestive heart failure*	*398.91, 402.01, 402.11, 402.91, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.x, 518.4*
	Diabetes	*250.x, 357.2, 362.0, and 366.41*
	Hypertension	*401.x, 402.x, 403.x, 404.x, and 405.x*
	Stroke TIA	*433,434, 435, 436*
	Vascular disease	*410,411,412, 413, 414, 443.8, 443.9*
Major Charlson's Comorbidity Index diagnosis	*Myocardial Infarction*	*410, 412*
	CHF	*428*
	Cerebrovascular disease	*430-438*
	COPD	*490-496, 500-505, 506.4*
	Paralysis	*342, 344.1*
	Chronic Renal failure	*582, 585, 586, 588, 583.0 – 583.7*
	Ulcers	*531-534*
	Cirrhodites	*5712, 5714, 5715, 5716*
	AIDs	*042,044*
	Metastatic tumor	*196.0-199.1, 196.x*
INR Monitoring	*Prothrombin time*	*V58.61, CPT codes 85610, 85611, 99363, and 99364*

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